"FORMULATION AND IN VITRO EVALUATION STUDIES ON ORAL FLOATIN MATRIX TABLETS OF RITONAVIR"

Dissertation submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY,

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In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY
IN
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Submitted by

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Under the Guidance of

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CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"*FORMULATION AND IN-VITRO EVALUATION STUDIES ON ORAL FLOATING MATRIX TABLETS OF* RITONAVIR "** submitted in the partial fulfillment for the degree of **MASTER OF PHARMACY** in Pharmaceutics, The Tamil Nadu Dr. M.G.R. Medical university, Chennai, is a bonafide work, which was carried out by **Mr. KANNEDHARA GOPALA RAO (Reg.No.261210806)** under my guidance and supervision during the academic year 2013-2014.

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DECLARATION

The work presented in this dissertation entitled **"*FORMULATION AND IN VITRO EVALUATION STUDIES ON ORAL FLOATIN MATRIX TABLETS OF* RITONAVIR"** was carried out by me under the guidance of, **Mr.K.G.PARTHIBAN,M.Pharm.,(Ph.D).,**Professor in Department of Pharmaceutics, J.K.K.Munirajah Medical Research Foundation College of Pharmacy, and Komarapalayam. This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other university.

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LIST OF ABBREVIATIONS USE

%	-	Percentage
°C	-	Temperature on Celsius scale
API	-	Active pharmaceutical ingredient
Conc.	-	Concentration
CP	-	Centi-poise
CRDDS	-	Controlled release drug delivery system
DDS	-	Drug delivery system
FT-IR	-	Fourier Transform Infra Red
G/ml	-	Grams per milliliter
GIT	-	Gastro intestinal tract
Gm	-	Gram
HPMC	-	Hydroxy propyl methyl cellulose
L	-	Liter
m Pa S	-	milli Pascals seconds
M	-	Molarity
Min	-	Minutes
N	-	Normality
No.	-	Number
pH	-	Negative log of Hydrogen ion concentration
pKa	-	Negative log of acid dissolution constant

Psi	-	Per square inch
R^2	-	Regression coefficient
RH	-	Relative Humidity
rpm	-	Rotation per minute
Rt	-	Retention time
SD	-	Standard deviation
Sem	-	Scanning electron microscopy
SEM	-	Standard error mean
SS	-	Stock solution
TK	-	Tyrosine kinase
UV	-	Ultra Violet
v/v	-	volume by volume
Vs	-	Verses
W/v	-	weight by volume
W/w	-	weight by weight
λmax	-	Absorption maxima
µg/ ml	-	Microgram per milliliter
µl	-	Microliter
µm	-	Micrometer

1. INTRODUCTION

The oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations. However, it is a well accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12 or even 24 hours is possible for many drugs that are absorbed uniformly from GI tract. Nevertheless this approach is not suitable for a variety of important drugs characterized by narrow absorption window in the upper part of GI tract i.e. stomach and small intestine.

The design of oral controlled drug delivery systems (DDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

The controlled release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug. Depending upon the manner of drug release they are classified as follows

1.1. CLASSIFICATION OF CONTROLLED DRUG DELIVERY SYSTEM [4, 27, 37]

A. Continuous release system: These systems release the drug for a prolonged period of time along the entire length of GIT with normal transit of the dosage form. The various systems under this category are:

I. Dissolution controlled release systems

II. Diffusion controlled release systems

III. Dissolution and diffusion controlled release systems

IV. Ion-Exchange resins – drug complexes

V. slow dissolving salts and complexes

VI. pH–dependent formulations

VII. Osmotic pressure controlled systems

VIII. Hydrodynamic pressure controlled systems

B. Delayed transit and continuous release system: These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage is fabricated to retain in the stomach and hence the drug present therein should be stable at gastric pH. Systems included in this category are:

I. Altered density systems

II. Mucoadhesive systems

III. Size-based systems

C. Delayed release systems: The design of such systems involve release of drug only at a specific site in the GIT.

The drugs contained in such system have following category:

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site, or
- Meant to exert local effect at a specific GI site.

The two types of delayed release systems are:

I. Intestinal release systems

II. Colonic release systems

Oral controlled release dosage forms have been developed for the past three decades due to their various benefit characteristics which includes.

Table No.1: Advantages

Benefit of oral controlled-release drug delivery systems	
Benefit	***Reason***
Therapeutic advantage	Reduction in drug plasma level fluctuations; maintenance of a steady plasma level of the drug over a prolonged period, ideally simulating an intravenous infusion of a drug ref
Reduction in adverse side effects and improvement in tolerability	Drug plasma levels are maintained within a narrow therapeutic window with no sharp peaks and with AUC of plasma concentration versus time comparable with total AUC from multiple dosing with immediate release dosage form.
Patient comfort and compliance	Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.
Reduction in health care cost	The total cost of the controlled release product could be lower than the immediate release product. With reduction in side effects the overall expense in disease management also would be reduced.

Despite several advantages associated with controlled drug delivery system, there are number of disadvantages present with this type of drug delivery system.

Table No.2: Disadvantages

Disadvantages of oral controlled-release drug delivery systems	
Disadvantage	***Reason***
Over dose	There is always possibility of sudden release of the total dose administered i.e. dose dumping, which may result in toxic manifestations.
Less flexibility in dose adjustments	The adjustment of dosage for controlled release dosage form is very difficult. The physician has less flexibility in adjusting the dosage regimens.
Side effects	Along with longer duration of action controlled release preparations shows long duration of side effects, especially if the patient is hypersensitive to the given medication.
Cost	The cost of unit dose of controlled therapeutic system is higher than the conventional dosage forms.

To overcome these problems and improve the efficacy of oral administration, some recent studies have reported that controlled oral drug delivery system with prolonged gastric residence time, such as floating dosage system have been proved to be advantages.

A gastrointestinal drug delivery system can be made to float in the stomach by a gelling process of hydrocolloid materials or by incorporating a floatation chamber with vacuum or gas. In this way bulk density less than that of gastric fluid is produced. However, most of the devices generating gas or gelling need time to be floated and this parameter must be checked carefully in order to prevent the dosage

form from transiting into the small intestine along with food before floating in stomach.

1.2. GASTRO-RETENTIVE DOSAGE FORMS (GRDF):[1,5,12,14,15,50]

These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

The gastric emptying time mainly depends upon the design of the dosage form and physiological state of the subject, which last from a few minutes to 12 hrs. The average gastric emptying time in human is 2-3 hrs through major absorption zone (stomach and upper part of the intestine), which leads to incomplete drug release from the DDS leading to diminished efficacy of the administered dose. So drugs which have stability problem, GRDF plays an important role. These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities.

GRDF will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time.

1.2.1. Anatomy and Physiology of Stomach: [44]

1.2.1. a) Anatomy:

The stomach is j- shaped organ located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach.

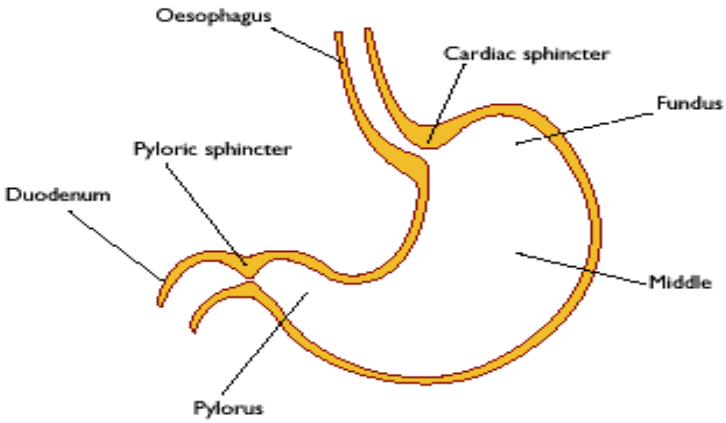


Figure No. 1: Anatomy of the stomach.

The stomach has four main regions:

1. Cardia
2. Fundus
3. Body and
4. Pylorus

The main function of the fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal region, to pass through the pyloric sphincter into the small intestine.

1.2.1. b) Physiology:

Various factors like absorption ability, presystemic clearance, gastric motility; gastrointestinal transit time and gastrointestinal emptying time will have an influence on the bioavailability of drug from the dosage form.

Absorption ability:

The absorption capability of various segments of gastrointestinal tract differs from each other. i.e. most of the absorption takes place in small intestine and lesser extent in colon and stomach. Unless drugs are absorbed equally in both the colon and in small intestine, the duration for most of the drugs is 3-8 hours. This will be the

major limiting factor for sustained release and controlled release drug delivery systems.

Presystemic clearance:

Even if the drugs that can be absorbed equally well throughout the gastrointestinal tract, bioavailability is significantly reduced by the site-specific changes in presystemic clearance. Degradation of the drug is also carried out by hydrolysis in the stomach, enzymatic digestion, and metabolism in the brush border of the gut wall and by the microorganisms.

Such degradation may leads to high variation in plasma drug concentration and poor absorption of drug in to the systemic circulation.

Gastric motility:

Gastric emptying occurs during fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintifc graphic studies determining gastric emptying rates revealed that orally administered controlled

release dosage forms are subjected to basically two complication, that of short gastric residence time and unpredictable gastric emptying rate.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action and potential contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

Gastrointestinal Transit Time:

Food content remains in each segment of the gastrointestinal tract for different periods of time. The resident time for both liquid and solid foods in each segment of the gastrointestinal tract is as reported by park.

Table No.3: Transit time of food in each segment of the gastrointestinal tract

Segment	*Liquid*	*Solid*
Stomach	10-30min	1-3 hours
Duodenum	< 60sec	< 60 sec
Jejunum and ileum	3 hours ± 1.5 hours	4 hours ± 1.5 hours
Colon	----------	20-50 hours

Since most of the drugs are absorbed from the upper part of intestine, the total effective time for the drug absorption is 3-8 hours. So one has to take most of the drugs 1-2 times a day.

1.2.1.c) Factors affecting the gastric emptying time:[32]

I. **State of the stomach**: gastric emptying time depends upon the fed state of the stomach, which increases the gastric emptying time as compared to unfed state.

II. Circadian rhythms**:** which are increased in day time and less during night, also affects the gastric retention time (GRT).

III. Size of the Meal: greater the energy content of the meal (carbohydrate and high fat content), longer the duration of emptying.

IV. Density of the oral dosage form: The density of the gastric fluid is reported to be 1.2g/cm. The density of the dosage form should be less than this for the buoyancy so that it is retained in the stomach for longer period of time.

V. Diseased state: State of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms.

VI. Drug therapy: Plays an important role in gastric emptying e.g. prokinetic drugs like cisapride and mosapride increase the gastric emptying time.

VII. Age: Increase in age decreases the gastric motility thereby increasing the gastric emptying time.

VIII. Posture: It was seen that the supine posture on the right side showed better results than on the left side.

1.2.1. d) Criteria for selection of drug candidate for GRDF: [32]

The gastric retentive drug delivery systems are suitable for following types of drug therapy:

I. Absorption from upper part of GIT: Drugs have a particular site for maximum absorption e.g. ciprofloxacin, whose maximum absorption is in the stomach only. The absorption of metformin hydrochloride is confirmed to small intestine only and the conventional sustained release dosage forms may be poorly bioavailable since absorption appears to diminish when the dosage form pass in to large intestine.

II. Drugs having low pKa, which remains unionized in stomach for better absorption.

III. Drugs having reduced solubility at higher pH e.g.captopri*l* and chlordiazepoxide and the bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms. e.g. doxifluridine, which degrades in small intestine.

IV. Local action as it is seen in the treatment of *H.Pylori* by amoxicillin and misoprostol for ulcers.

V. To minimize gastric irritation this may be caused by sudden increase of drug concentration in the stomach. E.g. NSAIDs.

VI. Improve effectiveness of particular drugs. E.g. antibiotics in the colon tend to disturb the microflora causing overgrowth of microorganisms like Clostridium difficile causing colitis.

1.3. GASTRO RETENTIVE DRUG DELIVERY SYSTEM: [55(b), 32, 45]

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Oral medication is generally considered as the first avenue investigated in the development of pharmaceutical formulations because of patient acceptance, convenience in administration and cost effective manufacturing processes. Oral route offers an attractive approach of drug targeting at the specific site within GI tract for certain types of drug.

1.3.1 Approaches to Gastric Retention:

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include:

a) Floating Systems: [23]

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

Floating systems can be classified into two distinct categories,

(A) effervescent

(B) non-effervescent systems.

b) Bio/Muco-adhesive Systems: [27]

Bio/Muco-adhesive systems are those which bind to the gastric epithelial surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Binding of polymers to the mucin/epithelial surface can be divided into three broad categories:

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

c) Swelling and Expanding Systems:

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as “plug type system” since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability and maintains its physical integrity for prolonged period.

d) High Density Systems

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, and iron powder.

e) Incorporation of Passage Delaying Food Agents:

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

f) Ion Exchange Resins: [33]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

g) Osmotic Regulated Systems:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components, drug reservoir compartment and osmotically active compartment.

1.3.2 Types of Floating Drug Delivery Systems (FDDS): [16, 42]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are:

A. Effervescent System

I. Gas generating system

1. Gastric bilayered floating tablets
2. Multiple unit type floating pills
3. Multi-unit type oral floating stages of floating mechanisam dosage system

II. Volatile liquid/vacuum containing system

1. Intragastric floating gastrointestinal drug delivery system
2. Inflatable gastrointestinal delivery system
3. Intragastric osmotically controlled drug delivery system

B. Non- Effervescent System

1. Single layer floating tablets

2. Alginate beads

3. Hollow microspheres

A. Effervescent System: [2]

Effervescent systems include use of gas generating agents, carbonates (sodium bicarbonate) and other organic acid (citric acid and tartaric acid) to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types.

I. Gas Generating Systems:

Intra Gastric Single Layer Floating Tablet or Hydro dynamically Balanced System (HBS)

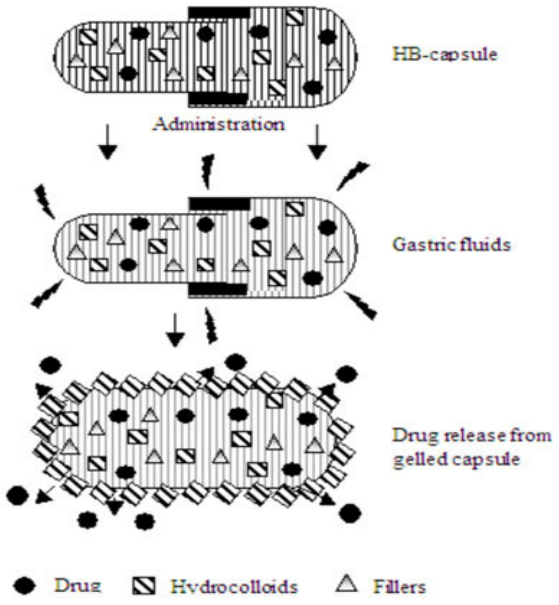


Figure No. 2: hydro dynamically balanced system

These are formulated by mixing the CO_2 generating agents and the drug within the matrix tablet (Fig. 2). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating

system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

1. Intra Gastric Bilayered Floating Tablets:

These are also compressed tablet and contain two layers for:

i) Immediate release layer and ii) Sustained release layer (Fig. 3).

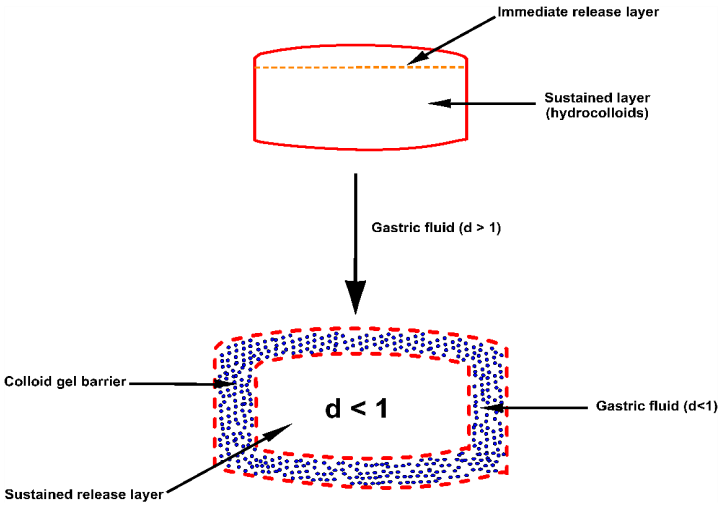


Figure No. 3: Intra Gastric Bilayer Floating Tablet.

2. Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swollen pill like balloon and float as the density decreases (Fig. 4&5).

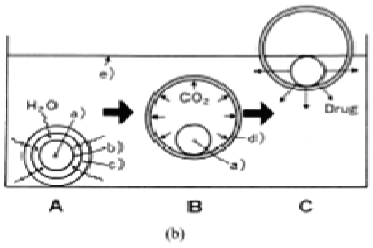


Figure No. 4

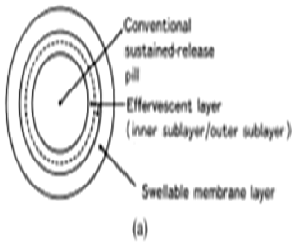


Figure No. 5

3. Multi-unit type oral floating Stages of floating mechanism dosage system

A Penetration of water

B Generation of CO_2 and floating Dissolution of drug

C Release of drug from the resorvoir

II. Volatile Liquid / Vacuum Containing Systems:

1. Intragastric Floating Gastrointestinal Drug Delivery System: [26]

This system can be made to float in the stomach because of flotation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment (Fig. 6).

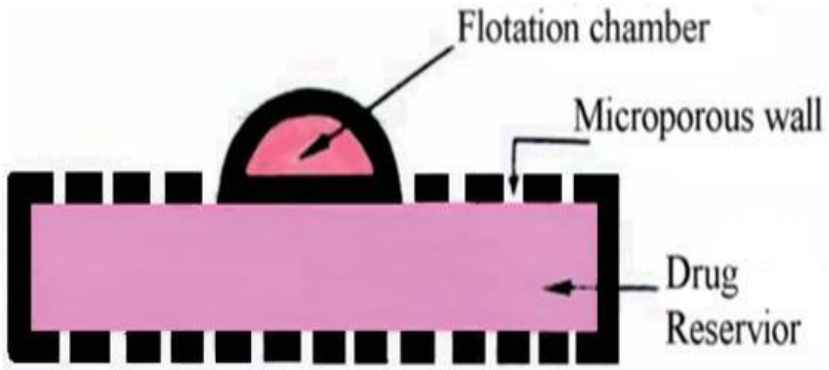


Figure No. 6: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid (Fig. 7).

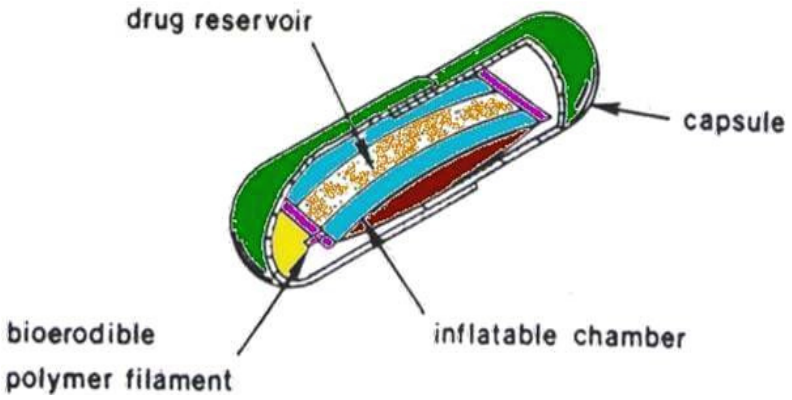


Figure No. 7: Inflatable Gastrointestinal Delivery System

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach (Fig. 8).

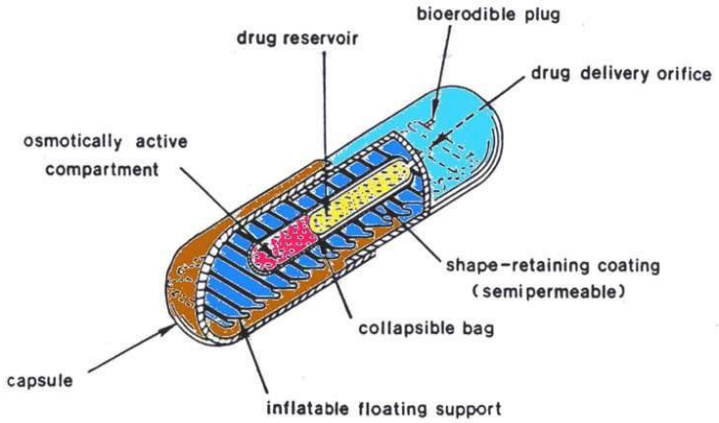


Figure No. 8: Intragastric Osmotically Controlled Drug Delivery System

B. Non Effervescent Systems:

The Non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethacrylates, polystyrenes and bioadhesive polymer such as chitosan and carbopol.

The various types of these systems are:

1. Single Layer Floating Tablets: [58, 49]

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. Alginate Beads: [47]

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hour.

3. Hollow Microspheres:

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with Drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Micro balloons were floatable *in-vitro* for 12 hours when immersed in aqueous media. Radio graphical studies proved that micro balloons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hours against peristaltic movements.

1.4.3 Application of FDDS: [32]

1. For treating local inflammation and stomach ulcers.

2. For treating *H. Pylori* associated ulcers.

3. In chronic diseases associated with frequent medication and prolonged medication, FDDS can be promising drug delivery system.

1.5 MATRIX SYSTEMS:[13,30,39,55]

A matrix is a uniform mixture of drug and excipients. e.g. polymer that is homogeneously fixed in solid dosage form.

The drug substance, which has a solubility S gm /cm^3 in the dissolution medium, is dispersed in the matrix which is insoluble in the dissolution medium, is dispersed in the matrix which is insoluble in the dissolution medium. The concentration of drug in the matrix is 'A' gm / cm^3**.** The matrix is porous, with a porosity of **'Є'** and diffusion coefficient of 'D_m'. The drug release from such system can be described by $dQ/dt = 2SD_mAt$. Liquid will intrude from the bulk liquid. The rate and extent of intrusion will follow the following equation:

$$\frac{dL}{dt} = \frac{-Qr2}{8\eta L} = -\frac{q}{L}$$

Where, L is the length of the intrusion at time t, r is the average radius of the pores, ŋ is the viscosity of the liquid and Q is a constant[21].

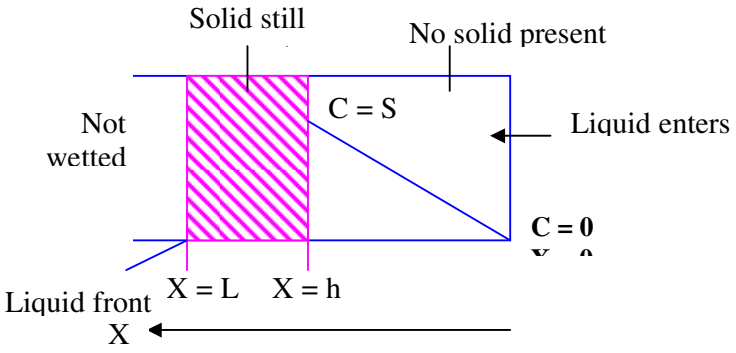


Figure No. 9: Dissolution of drug from a solid matrix

1.5.1. HYDROPHILLIC MATRIX SYSTEM:

A hydrophilic matrix controlled release system is a dynamic system composed of polymer wetting, polymer hydration and polymer dissolution. At the same time other soluble excipients or drug will also wet, dissolve and diffuse out of the matrix while insoluble materials will be hold in place until the surrounding polymer/ excipients / drug complex erodes or dissolves away.

The main principle is that a water-soluble binder, present throughout the tablet, partially hydrates on the outer tablet "**sink**" to form a gel layer. Throughout the

life of ingested tablet the rate of drug diffusion (if soluble) out of the wet gel and the rate of tablet erosion control the overall dissolution rate and drug availability.

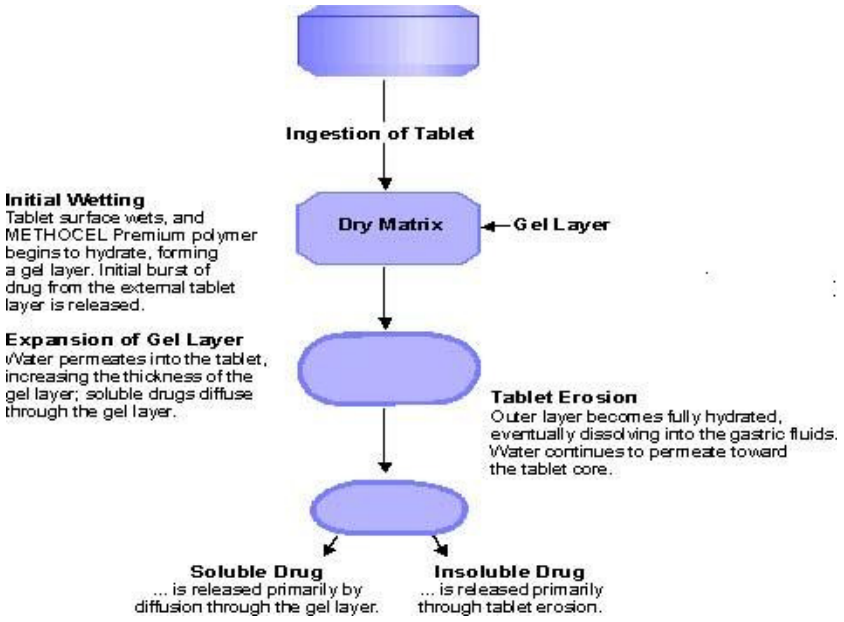


Figure No. 10 : Matrix System

.1.5.1.(a). ADVANTAGES OF HYDROPHILIC MATRIX SYSTEM: [21]-

A hydrophilic matrix system essentially consists of a drug dispersed in a water swelling viscous polymer. These systems offer a number of advantages over other sustained release technologies namely.

1. Simplicity of formulation.
2. High drug loading as high as 80 % is possible in many cases.
3. The system is usually inexpensive as the rate-controlling agent is usually a GRAS (generally accepted as safe) food polysaccharides.
4. Number of matrix former is available allowing development of formulations that meet special needs and avoid patent infringement.
5. The systems are eroded as they pass the GIT thus there are no accumulation of "Ghosts" or empty shells.

6. As system depends on both diffusion and erosion for drug release, release is not totally dependent on GI motility.
7. No specialized equipment is required which substantially reduces manufacturing costs.
8. Offer easy scalability and process validation due to simple manufacturing processes.
9. The above listed advantages overshadow the undesirable property of reducing release rates with time.

1.5.2. DISADVANTAGES OF HYDROPHILIC MATRIX SYSTEM

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.5.3. MATRIX TYPE: [22]

The most common controlled delivery system has been the matrix type such as tablets and granules, where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period.

Hydrophilic polymers are becoming more popular in formulating oral controlled release tablets, it is well documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time dependent profile. The release of a dissolved drug inherently follows near first order diffusion either an initially high

release rate, due to the dissolution of the drug present at the surface of the matrix followed by a rapidly declining drug release rate. The enhanced release rate observed at the beginning for the short time of release process is known as "**burst effect**" and is many a time undesirable since it may, have negative therapeutic consequences. After this burst effect, hydration and consequent swelling and/or erosion of related polymer occur. These phenomenons control the release process but with time, the diffusion path length increases and saturation effect is attained, resulting in a progressively slow release rate during the end of dissolution span.

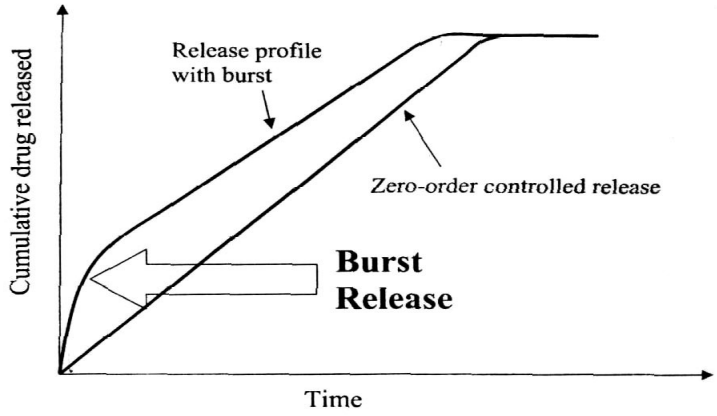


Figure No. 11: Schematic showing the burst effect in a zero-order

Drug delivery system:

In many controlled release formulations immediately upon placement in release medium, an initial large bolus of drug is release medium; an initial large bolus of drug is released before the release rate reaches a stable profile. This phenomenon is referred to as **burst release**.

1.5.4. Cause of burst release

1) Processing conditions
2) Surface characteristics of host material
3) Sample geometry
4) Host and drug interaction (surface adsorption)

5) Morphology and porous structure of dry material.

1.5.5. Prevention of burst release:

Several advanced technologies to avoid burst include

a) Surface extraction of active agent

Approaches have been taken to reduce the initial burst, such as extracting the drug formulation for a short period of time in vitro before using them in-vivo application. Burst effect is reduced because drug is removed from the outer layers of controlled release devices. E.g. Lee showed the effectiveness of surface extraction in reducing burst release of Oxprenolol HCl from P-HEMA hydrogen.

b) Coated surface

It is another method which prevents burst release is surface modification by additional coating steps to provide an outer layer with no drug. Colombo and co-workers have done extensive work in understanding the influence of exposed surface area on drug release. They defined a dimensionless parameter so, the swelling area number as

$$S_d = \frac{1}{D} \cdot \frac{dA}{dt} \text{-------- (2)}$$

Where,

dA/dt = rate of releasing area charge

D = drug diffusion coefficient

c) Drug loading distribution

Non uniform drug loading, i.e. the increasing concentrations away from surface overcome the growing rubbery gel layer. This gel layer typically leads to diminishing release rates with time in uniformly loaded gels.

d) Polymer morphology and composition

The polymer microstructure and hydrophilic/hydrophobic interaction also play an important role in determining drug distribution profiles and release characteristics.

e) Surface modification

To prevent burst release from porous polymer structures caused by solvent evaporation during processing many methods have been attempted which are based on changing the surface characteristics of the devices.

1.6. SWELLING CHARACTERISTICS OF POLYMER: [27]

The Peppa's plot is useful to determine whether the drug release from the matrix is controlled by swelling of the polymer or not. The Peppa's equation is

$$\log Q = \log (kt^{½}) \text{ ----------(3)}$$

$$\log Q = \log k + 0.5 \log t \text{ ----------(4)}$$

Where,

Q = amount of drug release in time t per unit area

k = release constant.

If the slope of a plot of log Q Vs log t is exactly 0.5, then the drug release occurs by perfect diffusion obeying Higuchi's and Fick's law. If it is in the range of 0.5 – 1, then the mechanism of release is diffusion and rate of diffusion is controlled by swelling of polymer. If it is bellow 0.5, then there is no swelling of matrix occur.

1.7. MECHANISM OF DRUG RELEASE FROM MATRIX SYSTEM: [46, 21]

When a hydrophilic matrix system containing a swellable glassy polymer comes in contact with an aqueous medium, the fall in glass transition temperature leads to an abrupt change from a glassy to a rubbery state, causing swelling of the polymer on the surface and formation of a hydrated gel. Drug release is controlled by

this gel diffusional barrier and/or by surface erosion of the gel. Surface leaching of the drug can lead to an initial burst, especially with highly soluble drugs.

Hydration of individual polymer chains leads to expansion in their end to end distance and radius of gyration to a new solvated state due to lowering of the polymer transition temperature, a sharp distinction between glassy and rubbery region is observed and the matrix increases in volume because of swelling.

When the system is hydrated to the core, the drug concentration falls below its solubility value and the release rate of the drug begins to decline. A concurrent increase in the thickness of the barrier layer with time increases the diffusion path length, further reducing the release rate. Drug release kinetic associated with this gel layer dynamics, range initially from Fickian to anomalous (Non-Fickian) and subsequently from quasi-constant (near zero order) to constant. Matrices of highly molecular weight polymers rarely shows all three regimens (Fickian, Non-Fickian and quasi-constant) of drug release because of a low chain disentanglement rate and insufficient external polymeric mass transfer.

Soluble drugs are primarily released by diffusion through aqueous filled porous network formed in the inert matrix former due to dissolution and erosion of the polymer from the surface. For poorly soluble drugs dispersed in inert polymer systems erosion is the primarily release mechanisms.

There are two major processes that control the drug release from swelling controlled matrix systems, these include:

1. Ingress of aqueous medium into the matrix followed by a hydration, gelation or swelling and
2. Matrix erosion.

Simultaneous occurrence of these processes leads to the formation of two fronts within the hydrating matrix, this are **a swelling front**, at the junction of the unhydrated glassy matrix and the hydrated matrix and **an eroding front** where the polymer is completely hydrated. Thickness of the diffusion layer, i.e. the distance between the two fronts, depends on the relative rates at which the swelling and erosion occurs.

If the polymer gels slowly, solvent can penetrate deep into the glassy matrix, thus dissolving the drug; therefore, gel layer thickness and its stability are crucial in controlling drug release. Numbers of techniques have been used to study the swelling of matrix tablets and to characterize the gel layer and front movement such as, optical imaging,^{1}H- NMR, pulsed filled gradient spin echo NMR, confocal laser scanning microscopy, cryogenic scanning electron microscopy and texture analysis. The gel layer thickness is determined by the relative position of the swelling and erosion front.

1.8. DRUG RELEASE MECHANISM FROM MATRICES: [29]

From time to time, various authors have proposed different types of drug release mechanisms from matrices. It has been proposed that drug release from the matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and / or the erosion of the gelatinous layer. However, it is worth mention that the release mechanism of a drug would depend on the dosage form selected, pH, and nature of the drug and of course, the polymer used.[11]

a) Zero order kinetics:

Drug dissolution from pharmaceutical dosage from that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = Kt \text{ --------- (5)}$$

Where,

W_0 = initial amount of drug in the pharmaceutical dosage form,

W_t = amount of drug in the pharmaceutical dosage form,

t = time,

K = Proportionality constant.

The pharmaceutical dosage form following this profile release the same amount of drug by unit of time and in this model can be explained by following equation:

$$Q_t = Q_0 + K_0 t \text{ ---------- (6)}$$

Where,

Q_t = Drug dissolved in time t,

Q_0 = Initial amount of drug in solution,

K_0 = Zero order rate constant.

OR,

$W = K.t$ (Xu and Sunada, 1995) --------- **(7)**

Where,

W is percentage drug release at time t,

K is the release rate constant

b) First order kinetics:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner. The dissolution phenomena implies a surface action, as can be seen by Noyes – Whitney equation,

$$\frac{dc}{dt} = K(C_s - C) \text{ ---------- (8)}$$

Where, C = Concentration of solute in time t,

C_S = solubility in equilibrium at experience temperature.

k =First order proportionality constant

Hixson and Crowell adapted the above equation as

$$\frac{Dw}{dt} = KS(C_s - C) \text{ ---------- (9)}$$

Where, w = amount of solute in solution at time t,

S = Solid area accessible to dissolution.

$$\log Q_t = \log Q_0 + K_1.t / 2.303 \text{ --------- (10)}$$

Where, Q_t = amount of drug release in time t,

Q_0 = initial amount of drug in solution,

K_1 = First order release constant.

Above equation also represents this model.

The pharmaceutical dosage form following this dissolution profile, such as those containing water soluble drugs in porous matrices release drug in a way that is proportional to amount of drug remaining in its interior in such a way that amount of drug released by unit of time diminish.

OR,

In (100 – W) = In 100 – k t (Singla and Medrata, 1988; and Sunada 1995)-- (**11**)

1.9. Definition of HIV:

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (**HIV/AIDS**) is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV).[1] During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system, making the person much more likely to get infections,

including opportunistic infections and tumors that do not usually affect people who have working immune systems.

HIV is transmitted primarily via unprotected sexual intercourse (including anal and even oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding.[2] Some bodily fluids, such as saliva and tears, do not transmit HIV.[3] Prevention of HIV infection, primarily through safe sex and needle-exchange programs, is a key strategy to control the spread of the disease. There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease, these medications are expensive and may be associated with side effects.

Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a $CD4^+$ T cell count below 200 cells per μL or the occurrence of specific diseases in association with an HIV infection. In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%),cachexia in the form of HIV wasting syndrome (20%) and esophageal candidiasis. Other common signs include recurring respiratory tract infections.

Opportunistic infections may be caused by bacteria, viruses, fungi and parasites that are normally controlled by the immune system. Which infections occur partly depends on what organisms are common in the person's environment. These infections may affect nearly every organ system.

People with AIDS have an increased risk of developing various viral induced cancers including Kaposi's sarcoma, Burkitt's lymphoma, primary central nervous system lymphoma, and cervical cancer. Kaposi's sarcoma is the most common cancer occurring in 10 to 20% of people with HIV. The second most common cancer is lymphoma which is the cause of death of nearly 16% of people with AIDS and is the initial sign of AIDS in 3 to 4%. Both these cancers are associated with human herpes virus. Cervical cancer occurs more frequently in those with AIDS due to its association with human papillomavirus (HPV).

Additionally, people with AIDS frequently have systemic symptoms such as prolonged fevers, sweats (particularly at night), swollen lymph nodes, chills, weakness, and weight loss. Diarrhea is another common symptom present in about 90% of people with AIDS. They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers

Classification of Anti Viral drugs:

Agents to treat Herpes Simplex Virus (HSV) & Varicella Zoseter Virus (VZV) infections

- Acyclovir, Valcyclovir, Famciclovir, Penciclovir, Trifluridine.

Agents to treat Cytomegalovirus (CMV) infections

- Ganciclovir, Valganciclovir, Cidofovir, Foscarnet, Fomivirsen.

Antiretroviralagents:

Nucloside Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine, Didanosine, Lamivudine, Zalcitabine, Stavudine, Abacavir.

Antiretroviralagents:

Nucleutide inhibitors

- Tenofovir

Antiretroviralagents:

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Nevirapine, Delaviridine, Efavirenz.

Antiretroviralagents:

Protease Inhibitors

- Saquinavir, Ritonavir, Lopinavir, Indinavir, Nelfinavir, Ampernavir.

Fusion Inhibitors

- Enfuvirtide (HIV), Docosanol (HSV).

Anti-Hepatitis agents

- Lamivudine, Ribavirin, Pegylated interferon alpha, Interferon alpha, Adefovir.

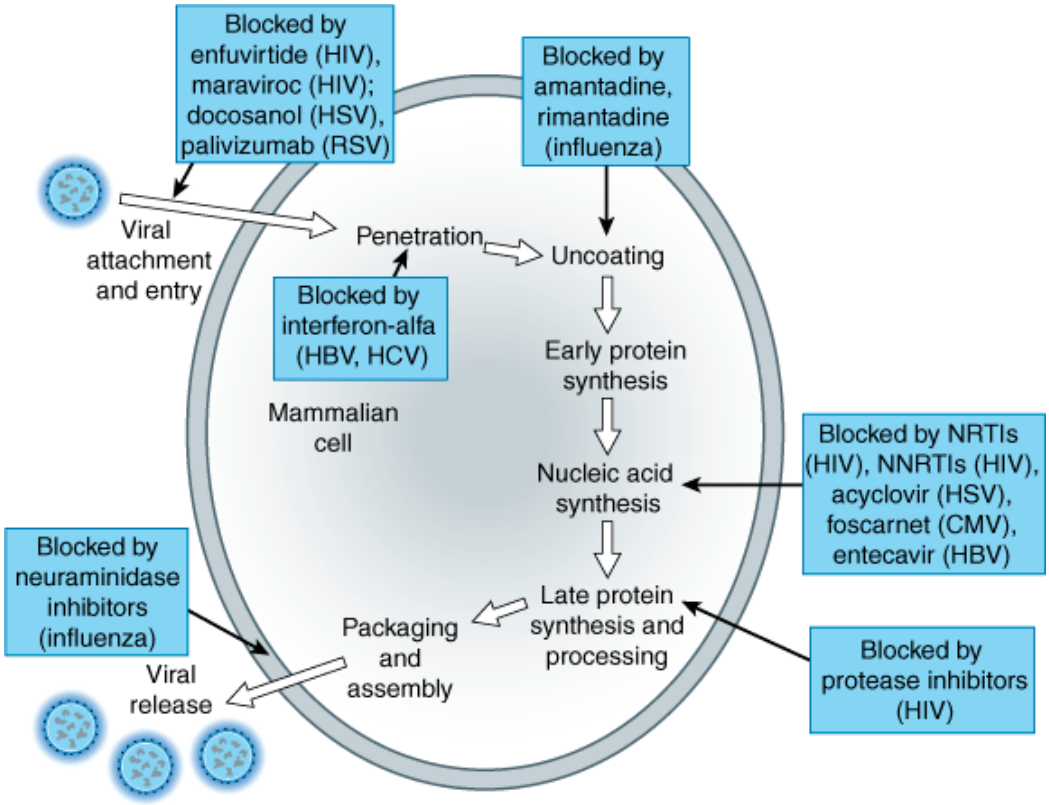
Anti-Influenza Agents

- Amantadine, Rimantadine, Zanamivir, Oseltamivir.

Other Antiviral agents

- Palivizumab, Imiquimo

The major sites of antiviral drug action



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

2. LITERATURE REVIEW

Syed Ershad *et al.,* (2013) prepared Floating microspheres of Ritonavir by ionic gelation method with an aim of increasing the gastric residence time and for controlled release. Sodium alginate, polymeric mixture of Sodium alginate and xantham gum were used as polymers. Sodium bicarbonate was used as the gas-forming gent. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapment efficiency, morphology and in vitro release study. These results indicated that the release rate was found to decrease with increase in concentration of coating material applied. The wall thickness of microspheres was found to be increased with the increase in concentration of coating material applied. The floating microspheres followed zero order kinetics and the mechanism of drug release was governed by peppas model.

K.P.R Chowdhary *et al.,* (2011) prepared, characterized and evaluated starch phosphate, a new modified starch as a carrier in solid dispersions for enhancing the dissolution rate of ritonavir. The feasibility of formulating solid dispersions of ritonavir in starch phosphate into compressed tablets with enhanced dissolution rate was also investigated. Starch phosphate was prepared by reacting starch with di-sodium hydrogen orthophosphate anhydrous at elevated temperatures. It was insoluble in water and has good swelling (400%) property without pasting or gelling when heated in water. Solid dispersions of ritonavir in starch phosphate were prepared by solvent evaporation method employing various weight ratios of drug: starch phosphate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of ritonavir when compared to pure drug. A 58.34

and 94.41 fold increase in the dissolution rate (K1) of ritonavir was observed with solid dispersions SD-4 and SD-5 respectively. The DE30 was also increased from 6.80% in the case of ritonavir pure drug to 76.25% and 84.05% in the case of these solid dispersions. Ritonavir (50 mg) tablets were prepared employing ritonavir alone and its solid dispersions SD-3 and SD-4 by wet granulation method and were evaluated. Ritonavir tablets formulated employing its solid dispersions in starch phosphate gave rapid and higher dissolution rate and DE30 when compared to plain and commercial tablets. A 9.95 and 28.14 fold increase in the dissolution rate (K1) was observed with tablet formulations containing solid dispersions SD-3 and SD-4 respectively when compared to plain tablets.

M.S. Hasoliya *et al*., (2012) prepared Floating microspheres of Ritonavir by simple dripping method with an aim of increasing the gastric residence time and for controlled release. A polymeric mixture of Sodium alginate and hydroxy propyl methyl cellulose was used. Sodium bicarbonate was used as the gas-forming gent. The solution was dropped to 1% calcium chloride solution containing 10 % acetic acid for carbon dioxide release and gel formation. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapped, morphology and *in-vitro* release study. Effect of sodium bicarbonate on the above mentioned parameters were evaluated and it was found that the sodium bicarbonate had a pronounced effect on various parameters. The enhanced buoyancy and controlled release properties of sodium bicarbonate containing microspheres made them an excellent candidate for floating dosage form.

Kanagala Vijayasri *et a l.,* (2013) prepared and evaluated montmorillonite (natural clay material) for enhancing the dissolution rate of drug by formulating solid

dispersions of ritonavir in montmorillonite into compressed tablets. Solid dispersions of ritonavir in montmorillonite were prepared by solvent evaporation method employing various weight ratios of drug: montmorillonite such as 1:1(SD-1), 1:2(SD-2), 1:4(SD-3) and 1:7 (SD-4). The tablets were evaluated. Prior to compression, the pre-compression parameters showed satisfactory flow properties. Post-compression parameters showed that all tablet formulations had acceptable mechanical properties. The compatibility of the drug in the formulation was confirmed by IR and DSC studies. Ritonavir tablets formulated employing its solid dispersion in montmorillonite gave rapid and higher dissolution rate and DE30 when compared to plain tablets. A 14, 12 and 8 fold increase in the dissolution rate (k1) was observed with tablet formulations containing solid dispersions SD-1, SD-2 and SD-3 respectively when compared to plain tablets

K.P.R. Chowdhary *et al.,* (2012) comparatively evaluated three commercially available DCVs namely Lubritose AN, Lubritose SD, Lubritose MCC and one laboratory made DCV namely starch phosphate, a new modified starch in the formulation development of three antiretroviral drugs by direct compression method. Tablets of (i) Efavirenz (100 mg) (ii) Ritonavir (100 mg) and (iii) Stavudine (30 mg) were formulated employing the four directly compressible vehicles and the tablets were evaluated for various physical properties and dissolution rate. All the tablets gave rapid dissolution of the contained drug. The dissolution was complete (100%) within 15 – 30 min with all the drugs and the dissolution was much higher than the official requirement in each case. Stavudine tablets exhibited faster dissolution than those of efavirenz and ritonavir with all the four DCVs. Hence these DCVs are recommended for the preparation of tablets of antiretroviral drugs by direct compression method.

Rabhi Narayan parhi *et al.,* (2013) developed a floating drug delivery system of ritonavir (RN) in order to prolong the gastric residence time and increase its bioavailability. The floating tablets of RN were prepared by direct compression technique, using polymers such as different grades of hydroxypropyl methylcellulose (HPMC, Methocel E15LV, E50LV, K100LV and K4M) and polyvinyl pyrrolidone (PVP K30). Sodium bicarbonate was used as gas releasing agent. The formulations were optimized on the basis of matrix integrity, duration of floating, swelling behavior and in vitro drug release. Except series FA, where floating time was 10 hr, other series such as FB, FC and FD were showing more than 12 hr of floating time. The mechanism of RN release from the floating tablets for FA, FB and FC series is anomalous diffusion transport and follows zero order kinetics, but FD series indicated Higuchi kinetics with release rate exponent (n) of 0.44. Further, the scanning electron microscopy showed porous structured formed on the tablet surface at different times (0, 3, 6, 9 and 12 hr) of dissolution for the selected batch FC3. Finally, FC3 batch showed no significant change in above parameters after storage at room temperature (28-32°C), 40°C and 50°C for one month.

Raju B *et al.,* (2012) studied and developed ritonavir is an antiretroviral drug with activity against Human Immunodeficiency Virus (HIV) type 1. In the present work an attempt is being made to provide for parenteral drug delivery with having improved therapeutic index for Ritonavir and anintention to develop a stable and effective parenteral formulation, containing the drug Ritonavir. Ritonavir is practically insoluble in water and unstable at higher temperature. The effects of various co solvents in the solubility of Ritonavir have been evaluated. Ritonavir was tried with co solvents such as Sodium-p-hydroxy benzoate, Sodium glycinate and Sodium thiocyanate. The drug was made into injection formulation for administered

as a SVP. Various batches of Ritonavir injection formulation were prepared in order to assess the influence of heat, light, atmospheric oxygen and antioxidant on the stability of the drug and the formulations were also subjected to accelerated stability test. Out of all trials, formulation containing Sodium thiocyanate was found to be more soluble, stable and passed all tests satisfactorily.

Chandira Margret R *et al*., (2010) developed floating tablets of Itopride hydro chloride, a novel pro kinetic drug, which after oral administration are designed to prolong the gastric residence time and thereby increase drug bioavailability and drug release rate. This would help in promoting gastro intestinal transit and speed up gastric motility and thereby it will relieve the symptoms associated with it. Floating tablets were fabricated using direct compression method containing itopride hydrochloride, polymers HPMC K100M, HPMC K15M and carbopol 934P along with gas generating agent sodium bicarbonate and citric acid. The addition of carbopol aided in the reduction of drug dissolution due to their hydrophobic nature. The concentration of these agents was also optimized to get desired controlled release of drug. The floating tablet formulations were evaluated for physical characterization, assay, swelling index, *in-vitro* drug release, hardness, friability and weight variation. The results indicated that gas powered floating tablets of Itopride hydrochloride containing 125mg HPMC K 100M, 40 mg HPMC K 15M and 40 mg carbopol provides a better option for 24 hrs release action and improved bioavailability mechanism.

Margret Chandira *et al.,* (2009) Prepared Diltiazem Hydrochloride undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, which results in less than 4% of its oral dose being excreted unchanged in urine. Suffers from poor bioavailability (~30% to 40%) owing to an important first pass metabolism.

It has an elimination half-life of 3.5 hrs and an absorption zone from the upper intestinal tract. Thus the present work is aimed to formulate floating tablets of Diltiazem Hydrochloride using an effervescent approach for gastro retentive drug delivery system. Floating tablets were prepared using direct compression technique using Hydrophilic polymer like HPMC K4M, HPMC K15M and hydrophobic polymer like Ethyl cellulose as matrix materials in various quantities (%w/w), sodium bicarbonate, citric acid, magnesium stearate, talc and lactose in varying ratio to formulate the floating tablets. Observations of all formulations for physical characterization had shown that, all of them comply with the specification of official pharmacopoeias and/or standard reference. It was observed that tablets of batch F6 followed the results obtained, it was concluded that the formulation F6 is the best formulations as the extent of drug release was found to be around 99.81 % at the desired time 12 hrs.

Desai.S *et al*., (1993) studied A novel floating controlled-release drug delivery was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. The buoyancy was attributed to air and oil entrapped in the agar gel network. A floating controlled-release 300mg theophylline tablet having a density of 0.67 was prepared and compared *in-vitro* and *in vivo* to Theo-dur. The *in-vitro* release rate of the floating tablet was slower. *In-vivo* scintigraphic studies for a floating and a heavy nonfloating tablet, under fasting and nonfasting conditions, showed that the presence of food significantly increased the gastric retention time for both tablets, and tablet density did not appear to make a difference in the gastric retention time. However, the positions of the floating and nonfloating tablets in the stomach were very different. Bioavailability studies in human volunteers under both fasting and nonfasting conditions showed results comparable to those with Theo-dur.

The floating controlled-release theophylline tablet maintained constant theophylline levels of about 2 mg/mL for 24 hr, which may be attributable to the release from the agar gel matrix and the buoyancy of the tablet in the stomach.

Ravi Kumar *et al*., (2009) development and evaluation of floating tablets of famotidine which, after oral administration, are designed to prolong the gastric residence time, increase drug bioavailability and target the gastric ulcer. A floating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxypropyl methylcellulose (HPMC) and carbopol 934P. The formulations were optimized for the different viscosity grades of HPMC, carbopol 934P and its concentrations and combinations. The results of the *in-vitro* release studies showed that the optimized formulation (F12) could sustain drug release (98%) for 24 h and remain buoyant for 24 h. The optimized formulation was subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation. Optimized formulation (F12) showed no significant change in physical appearance, drug content, total buoyancy time or in vitro dissolution study after storage at 45 °C/75% RH for three months. Finally the tablet formulations found to be economical and may overcome the draw backs associated with the drug during its absorption.

Shishu, Gupta N, Aggarwal N *et al*., (2007) developed and evaluated the single unit floating tablets of 5-FU which, after oral administration, are designed to prolong the gastric residence time, increase drug bioavailability and target the stomach cancer. **Methods:** A floating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxypropyl

methylcellulose (HPMC) and Carbopol 934P. The prepared tablets were evaluated in terms of their physical characteristics, *in vitro* release, buoyancy, buoyancy lag-time and swelling index. The formulations were optimized for the type of filler, like lactose, microcrystalline cellulose (MCC) and dicalcium phosphate (DCP) as well; different viscosity grades of HPMC and concentrations. **Results**: The results of the *in-vitro* release studies showed that the optimized formulation could sustain drug release for 24 h and remain buoyant for 16 h. When these dissolution profiles were subjected to various kinetic release investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation.

R Garg *et al*., (2008) studied that Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. On the other hand, incorporation of the drug in a controlled release gastro retentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastro retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastro retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Controlled gastric retention of solid dosage form may be achieved by the mechanisms of floatation, mucoadhesion,

sedimentation, expansion or by a modified shaped system. The purpose of this paper is to review the recent literature and current technology used in the development of gastro retentive dosage forms.

Patel Geeta M *et al*., (2007) studied Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. From immediate release to site-specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for the prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastro retentive delivery systems.

Abdul Sayeed *et al*., (2011) development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Floating tablets are the systems which are retained in the stomach for a longer period of time and there by improve the bioavailability of drugs. Floating tablets were prepared using directly compression technique using polymers like HPMC K4M HPMC K15M and HPMCK100M for their gel forming properties.

Peterson Bhoi *et al.*, (2010) developed floating matrix drug delivery system of Diclofenac sodium to prolong gastric residence time and increase its bioavailability. Floating matrix tablets containing 100 mg Diclofenac sodium were developed using different bees wax combinations. The tablets were prepared by melt granulation technique, using polymers such as Hydroxy propyl methyl cellulose (HPMC K15M), ethyl cellulose, bees wax alone or in combination with Cetyl alcohol and other

standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate on floating properties were investigated. The formulation was optimized on the basis of acceptable tablet properties, floating lag time, and total duration of floating and in vitro drug release. The resulting formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. The results of dissolution studies, floating lag time indicates that formulations F6 exhibited good and controlled drug release. Applying the linear regression analysis and model fitting, the selected formulation F6 showed diffusion coupled with erosion drug release mechanism, followed first order kinetic**s.**

Patel DM *et al.,* (2011) describes an influence of ratio of Gelucire 43/01(hydrophobic) to hydroxypropyl methylcellulose K4M (HPMC K4M) (hydrophilic) and different fillers on release of famotidine from gastro-retentive tablets using 3(2) full factorial design. Ratio of Gelucire 43/01 to HPMC K4M (X(1)) and the type of filler (X(2)) were selected as independent variables while buoyancy lag time (BLT), drug release at 1h (Q(1)), 6h (Q(6)), and the 12h (Q(12)) were selected as dependent variables. Gastro-retentive tablets of famotidine were prepared by a solvent free melt granulation technique using Gelucire 43/01 as a hydrophobic meltable binder. HPMC K4M and sodium bicarbonate were used as matrixing agent and gas-generating agent, respectively. Prepared tablets were evaluated for *in-vitro* dissolution, *in-vitro* buoyancy, friability, hardness, and drug content and weight variation. Dissolution data were fitted to various models to ascertain kinetics of drug release. The data were analyzed using regression analysis and analysis of variance. All formulations (F (1)-F (9)) showed floating within 3min and had total floating time of more than 12h. It was observed that a type of filler and the ratio of Gelucire 43/01

to HPMC K4M had significant influence on buoyancy lag time (P = 0.037) and Q (6) (P = 0.011), respectively without significant influence on Q (1) and Q (12).Formulation F (5) was selected as an optimum formulation as it showed more similarity in dissolution profile with theoretical profile (Similarity factor, f (2) = 83.01). The dissolution of batch F (5) can be described by zero order kinetics (r (2) = 0.9914) with anomalous (non-Fickian) diffusion as a release mechanism (n = 0.559). The difference observed in *in-vitro* release profile after temperature sensitivity study at 40°C for 1 month was insignificant.

Manoj N. Gambhire et al (2007) developed a floating drug delivery system of diltiazem hydrochloride (DTZ) to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxypropylmethylcellulose (HPMC, Methocel K100M CR), Compritol 888 ATO, alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate and succinic acid on drug release profile and floating properties were investigated. A 3^2 factorial design was applied to systematically optimize the drug release profile. The amounts of Methocel K100M CR (X_1) and Compritol 888 ATO (X_2) were selected as independent variables. The time required for 50% (t_{50}) and 85% (t_{85}) drug dissolution were selected as dependent variables. The results of factorial design indicated that a high level of both Methocel K100M CR (X_1) and Compritol 888 ATO (X_2) favors the preparation of floating controlled release of DTZ tablets. Comparable release profiles between the commercial product and the designed system were obtained. The linear regression analysis and model fitting

showed that all these formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (*r*). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

MD. Tabasum *et al.,* (2013) aimed to work on preparation and evaluation of diclofenac sodium controlled release matrix tablets using various proportions of natural polymer Abelmoschusesculentus mucilage powder (i.e; Drug: Polymer ratio-1:0.25,1:0.5,1:1,1:1.5,1:2) as release controlling factor by Wet Granulation method. The tablets were evaluated for various parameters like friability, weight variation, hardness, drug time, content uniformity. In vitro drug release characteristics of dosage form was evaluated in 6.8 pH phosphate buffer. All the formulations followed zero order kinetics along with diffusion mechanisms. From In vitro release data, formulation F4 containing Drug: Polymer (1:1.5) showed maximum drug release of 99.8%. All the formulations F1 to F5 undergo Non-Fickian diffusion or Enomalous diffusion mechanism. Analysis of drug release rate from matrix system indicated drug was release by super case-II transport mechanism.

G. Rajalakshmi *et al*., (2011) prepared oral effervescent tablets of diclofenac potassium. Six different formulations were prepared using different diluents, carbonates by wet granulation and direct compression method. The prepared tablets were evaluated for various pre compression characteristics (like angle of repose, bulk density, tapped density, cars index and hausner's ratio) and post compression characteristics (like weight variation, hardness friability ,drug content, disintegration, CO2 content, effervescent time, particle size and in vitro dissolution studies). The dissolution test was carried out in SIF without enzymes, 0.1N HCl and pH 4.8 acetate

buffers. Among all the formulations, its F3 formulations were better in all the terms of precompression and post compression parameters. In F3 formulations, F3A (by direct compression) and F3B (by wet granulation method) were there. F3B (composed of active dextrates (Emdex), citricacid, tartaric acid, effersoda and arginine) had given good pre formulation and post compression studies as F3A. Even the drug release in the medium SIF pH6.8 without enzymes was 99.2% when compared to F3A (98.7%) and marketed tablet (98%).It had all the qualities of a good effervescent tablet, based on this F3B formulation was selected as the best formulation, and it was charged for stability studies. It had given better release profile in all the mediums when compared to marketed conventional tablet (SUPANAC). A better therapeutic objective can be obtained by formulating effervescent tablet of diclofenac potassium that may help in obviating the demerits of slow release and slow absorption, gastrointestinal side effects of normal tablets

Chandrasekhara rao Barru *et al*., (2012) prepared Ibuprofen by Direct compression method, 4 formulations (F1 to F4) floating tablets of Ibuprofen were prepared using variable concentrations of HPMCE5M and Carbopol940,buoyancy lag time and the total floating time was studied for all the formulations, The compatibility evaluations were performed by DSC analysis. Studies imply that polymers are compatible with each other. There was no interaction found between polymer and drug. The research was undertaken with the aim to formulate and characterize the sustained release floating tablets of Ibuprofen using HPMCK4M and Carbopol 940 as polymers.

Kurnal *et al*., (2011) prepared a gastro retentive drug delivery system of Mebendazole. Chitosan and hydroxypropyl methyl cellulose of various viscosity were used. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of

citric acid and stearic acid on drug release profile and floating properties were investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. The specific s tudy was carried out to formulate such a dosage form that can neutralize the acidity locally in the stomach. The granulation was formed by Fluidized bed processor in which top spray technique was adopted for forming the granules.

Patel UK *et al., (*2008) developed amlodipine besylate effervescent floating tablets in ten different formulations (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms. F10 formulation showed maximum floating time of 24 hours and gave slow and maximum drug release of Amlodipine besylate spread over 24 hours and whereas Amlodipine besylate released from marketed tablet was rapid and maximum within 12 hours.

Rupavath Mahendar *et al.,* (2012) developed Gastro retentive floating matrix tablets to increase the gastric residence time of the drug after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma concentration and improving bioavailability. With the above objective, floating tablets containing Stavudine without the gas generating agent was designed for the treatment of HIV and AIDS. The matrix tablets were prepared by using natural polymer such as pullulan gum. The drug release kinetics study reveals that the formulations follow first order release with diffusion mechanism. In vivo x-ray studies showed the gastric residence time of the tablet up to 8 hours. The release and floating was depends on the polymer proportion in the matrix tablets. The

formulations were evaluated for in vivo floating time which shows the floating time up to 12 hours. The DSC and FTIR study shows that there is no drug polymer interaction.

CH.Swarna kamala *et al.,* (2012 formulated and evaluated gastro retentive floating drug delivery system containing gabapentin in the form of tablets using polymers like HPMC K100M, HPMC K15M, Polyox WSR 303 and sodium bicarbonate as gas generating agent. The tablets were prepared by direct compression method. The tablets were evaluated for the pre and post compression parameters such as weight variation, thickness, friability, hardness, drug content, in vitro buoyancy studies, and *in vitro* dissolution studies and results were within the limits. The in-vitro dissolution studies were carried out in a USP type-II apparatus in 0.1 N HCl. Among all the formulations (F1 to F9) prepared, batch F7 was the best formulation which showed buoyancy lag time 6sec and the tablet remained buoyant for > 24h. At all the strengths of the polymer tested combination of HPMC K100M and POLYOX WSR 303 (2:1) gave relatively slow release of gabapentin over24 h when compared to other formulations. The in-vitro data is fitted in to different kinetic models and the best-fit was achieved with the Higuchi model. The optimized formulation F7 followed first order release kinetics followed by non fickian diffusion.

3. AIM AND PLAN OF WORK

Aim:

The present research work was to develop a floating drug delivery system of ritonavir (RN) in order to prolong the gastric residence time and increase its bioavailability. Ritonavir is moderately weekly acidic drug, the stomach is the major absorption site for the drug. So by increasing the GRT of the drug, the bioavailability can be increased

The formulation may remained in the stomach and / or upper part of GIT for prolonged period of time thereby giving sufficient time for drug candidate to achieve maximum bioavailability(**Moumita Biswas2013),** and reduce unwanted side effects by minimizing or avoiding drug release at unfavorable site.

Objective:

The objective of the present work is to formulate and evaluate oral floating matrix tablets of Ritonavir 100mg, using hydrophillic polymers such as HPMC K4M, K15M and K100M of 100,150 and 200mg, by taking the single polymer in each formulation using Sodium bicarbonate as gas generating agent by direct compression technique to sustain the release of drug due to floating in stomach at acidic pH 1.2 up to 12 hrs.

3.1. PLAN OF WORK

1. Literature survey
2. Preformulation studies
   - Selection of drug.
   - Compatibility study using Fourier Transform Infrared Spectrophotometer.
   - Analytical characterization of the drug.
   - Selection of the excipients.
   - Characterization of the excipients.

3. Standard calibration curve of drug

4. Formulation development
   - Formulation of the floating tablet by Direct compression technique
   - Effect of the formulation variables on the drug release, swelling and floating properties.

4. Evaluation of tablets
   - Tablet characteristics.

     1) Weight variation

     2) Friability

     3) Hardness

     4) Drug content

- *In-vitro* Buoyancy study.
- Water uptake studies.
- *In-vitro* drug release studies of tablets.

5. Study of drug release kinetics.

6. Stability study of the optimized

FLOW CHART OF WORK

Selection of drug

↓

Compatibility study between drug and polymers

↓

Analytical characterization of the drug by determining characterization of drug

↓

Selection of excipients

↓

Characterization of the excipients

↓

Preformulation studies

↓

Preparation of ritonavir floating tablets by direct compression technique

↓

Evaluation of floating tablets

↓

Drug release kinetics

↓

Stability studies of optimized formulation

4. MATERIALS AND METHODS

Materials:

Table No.4: List of Chemicals Used

SR.NO.	NAME OF THE CHEMICAL	SUPPLIER
1.	RITONAVIR	YARROW CHEMICALS , MUMBAI
2.	HYDROXY PROPYL METHYL CELLULOSE K4M,K15M,K100M	YARROW CHEM PRODUCTS MUMBAI, INDIA.
3.	MICROCRYSTALLINE CELLULOSE	THOMAS BAKER Pvt Ltd, MUMBAI.
4.	SODIUM BICARBONATE	THOMAS BAKER Pvt Ltd, MUMBAI.
5.	POLYVINYL PYRROLIDONE K30	SD FINE CHEMICALS
6.	MAGNESIUM STEARATE	THOMAS BAKER Pvt Ltd, MUMBAI.
7.	TALC	THOMAS BAKER Pvt Ltd, MUMBAI.

Equipments:

Table No.5: List of Instruments Used

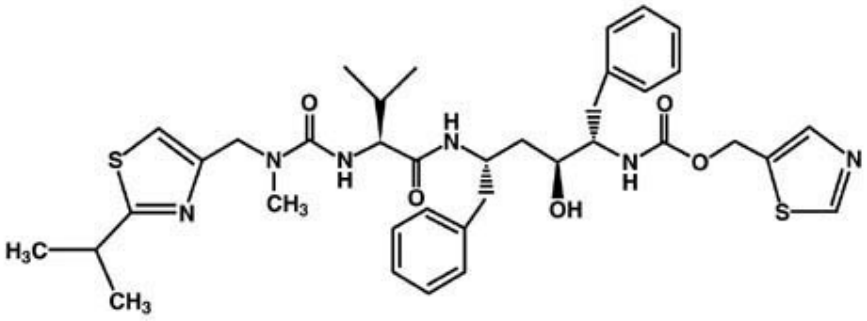
Instrument Used	Model No.	Make
FTIR Spectrophotometer	8400S	Shimadzu, Japan
UV–Visible Spectrophotometer	UV – 3000^{+}	LAB INDIA
Tablet Compression Machine	Mini Press	Rimek
Tablet Dissolution Tester USP (XXIII)	DS-8000	LAB INDIA
Environmental test chamber	JRIC – 11A	Oswald
Electronic Balance	AGN-303EC	AXIS
Tablet hardness tester	N.S	Monsanto
Roche's friabilator	N.S	Scientific
Hot air oven	PYROCON	York Scientific Ind., Mumbai
Digital pH meter	PHAN	LAB INDIA
Melting Point apparatus	N.S	Biotech India Ltd.

4.1 DRUG PROFILE

RITONAVIR

NORVIR (ritonavir) is an inhibitor of HIV-1 protease with activity against the Human Immunodeficiency Virus (HIV) type 1.

Structure of Ritonavir:



Molecular formula:

$C_{37}H_{48}N_6O_5S_2$

Relative Molecular Mass:

720.95

Chemical Name:

10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3, 6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oiacid,5thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]

Appearance:

Ritonavir is a white to light tan powder.

It is odourless.

It having a bitter metallic taste

Physical Properties of Ritonavir:

Physical State: Solid

Solubility: It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Storage: Store at room temperature

Half Life: 3-5hrs

CLINICAL PHARMACOLOGY

Pharmacokinetics:

The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-1 infected patients (CD4 greater than or equal to 50 cells per μL). See Table 6 for ritonavir pharmacokinetic characteristics.

Absorption:

The absolute bioavailability of ritonavir has not been determined.

Effect of Food on Oral Absorption:

After a single 600 mg dose under non-fasting conditions, in two separate studies, the soft gelatin capsule (n = 57) formulation yielded a mean ± SD area under the plasma concentration-time curve (AUC) of 121.7 ± 53.8. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 KCal; 14.5% fat, 9% protein, and 76% carbohydrate).

Metabolism:

Nearly the entire plasma radioactivity after a single oral 600 mg dose of 14C-ritonavir oral solution (n = 5) was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. *In vitro* studies utilizing human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M-2.

Elimination:

In a study of five subjects receiving a 600 mg dose of 14C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance

Table 6: Pharmaco kinetic parameters of Ritronavir

PK Parameter	Normal Healthy adults20 to 50 years	
	Mean	Coefficient of Variation (%)
Vß/F	91	0.41 ± 0.25 L/kg
t½		3-5hrs
Oral Clearance (CL/Fss; mL/min) [N = 61]	10	8.8 ± 3.2 L/h
CL/F	91	4.6 ± 1.6 L/h
CLR	62	< 0.1 L/h
RBC/Plasma Ratio		0.14
Percent bound		98-99%

Effects on Electrocardiogram

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 45 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) time-matched difference in QTcF from placebo after baseline correction was 5.5 (7.6) milliseconds (msec) for 400 mg twice-daily ritonavir. Ritonavir 400 mg twice daily resulted in Day 3 ritonavir exposure that was approximately 1.5 fold higher than observed with ritonavir 600 mg twice-daily dose at steady state.

PR interval prolongation was also noted in subjects receiving ritonavir in the same study on Day 3. The maximum mean (95% confidence interval) difference from placebo in the PR interval after baseline correction was 22 (25) msec for 400 mg twice-daily ritonavir.

Precautions:

Special Populations:

Gender, Race and Age:

No age-related pharmacokinetic differences have been observed in adult patients (18 to 63 years). Ritonavir pharmacokinetics have not been studied in older patients.

A study of ritonavir pharmacokinetics in healthy males and females showed no statistically significant differences in the pharmacokinetics of ritonavir. Pharmacokinetic differences due to race have not been identified.

Pediatric Patients:

Steady-state pharmacokinetics were evaluated in 37 HIV-1 infected patients ages 2 to 14 years receiving doses ranging from 250 mg per m^2 twice-daily to 400 mg per m^2 twice-daily in PACTG Study 310, and in 41 HIV-1 infected patients ages 1 month to 2 years at doses of 350 and 450 mg per m2 twice-daily in PACTG Study 345. Across dose groups, ritonavir steady-state oral clearance (CL per F per m2) was approximately 1.5 to 1.7 times faster in pediatric patients than in adult subjects. Ritonavir concentrations obtained after 350 to 400 mg per m2 twice-daily in pediatric patients greater than 2 years were comparable to those obtained in adults receiving 600 mg (approximately 330 mg per m2) twice-daily. The following observations were

seen regarding ritonavir concentrations after administration with 350 or 450 mg per m2 twice-daily in children less than 2 years of age. Higher ritonavir exposures were not evident with 450 mg per m2 twice-daily compared to the 350 mg per m2 twice-daily. Ritonavir trough concentrations were somewhat lower than those obtained in adults receiving 600 mg twice-daily. The area under the ritonavir plasma concentration-time curve and trough concentrations obtained after administration with 350 or 450 mg per m2 twice-daily in children less than 2 years were approximately 16% and 60% lower, respectively, than that obtained in adults receiving 600 mg twice-daily.

Renal Impairment:

Ritonavir pharmacokinetics have not been studied in patients with renal impairment, however, since renal clearance is negligible, a decrease in total body clearance is not expected in patients with renal impairment.

Hepatic Impairment:

Dose-normalized steady-state ritonavir concentrations in subjects with mild hepatic impairment (400 mg twice-daily, n = 6) were similar to those in control subjects dosed with 500 mg twice-daily. Dose-normalized steady-state ritonavir exposures in subjects with moderate hepatic impairment (400 mg twice-daily, n= 6) were about 40% lower than those in subjects with normal hepatic function (500 mg twice-daily,

(n = 6). Protein binding of ritonavir was not statistically significantly affected by mild or moderately impaired hepatic function. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. However, health care providers should be aware of the potential for lower ritonavir concentrations in patients with

moderate hepatic impairment and should monitor patient response carefully. Ritonavir has not been studied in patients with severe hepatic impairment.

Microbiology:

Mechanism of Action:

Ritonavir is a peptidomimetic inhibitor of the HIV-1 protease. Inhibition of HIV protease renders the enzyme incapable of processing the *gag-pol* polyprotein precursor which leads to production of non-infectious immature HIV-1 particles.

Antiviral Activity in Cell Culture:

The activity of ritonavir was assessed in acutely infected lymphoblastoid cell lines and in peripheral blood lymphocytes. The concentration of drug that inhibits 50% (EC50) value of viral replication ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC50 for low passage clinical isolates was 22 nM (n = 13). In MT4 cells, ritonavir demonstrated additive effects against HIV-1 in combination with either didanosine (ddI) or zidovudine (ZDV). Studies which measured cytotoxicity of ritonavir on several cell lines showed that greater than 20 μM was required to inhibit cellular growth by 50% resulting in a cell culture therapeutic index of at least 1,000**.**

Resistance:

HIV-1 isolates with reduced susceptibility to ritonavir have been selected in cell culture. Genotypic analysis of these isolates showed mutations in the HIV-1 protease gene encoding at amino acid substitutions I84V, V82F, A71V, and M46I. Phenotypic (n = 18) and genotypic (n = 48) changes in HIV-1 isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3 to

32 weeks. Substitutions associated with the HIV-1 viral protease in isolates obtained from 43 patients appeared to occur in a stepwise and ordered fashion; in sequence, these substitutions were position V82A/F/T/S, I54V, A71V/T, and I36L, followed by combinations of substitutions at an additional 5 specific amino acid positions (M46I/L, K20R, I84V, L33F and L90M). Of 18 patients for whom both phenotypic and genotypic analysis were performed on free virus isolated from plasma, 12 showed reduced susceptibility to ritonavir in cell culture. All 18 patients possessed one or more substitutions in the viral protease gene. The V82A/F substitution appeared to be necessary but not sufficient to confer phenotypic resistance. Phenotypic resistance was defined as a greater than or equal to 5-fold decrease in viral sensitivity in cell culture from baseline.

Cross-Resistance to Other Antiretroviral:

Among protease inhibitors variable cross-resistance has been recognized. Serial HIV-1 isolates obtained from six patients during ritonavir therapy showed a decrease in ritonavir susceptibility in cell culture but did not demonstrate a concordant decrease in susceptibility to saquinavir in cell culture when compared to matched baseline isolates. However, isolates from two of these patients demonstrated decreased susceptibility to indinavir in cell culture (8-fold). Isolates from 5 patients were also tested for cross-resistance to amprenavir and nelfinavir; isolates from 3 patients had a decrease in susceptibility to nelfinavir (6- to 14-fold), and none to amprenavir. Cross-resistance between ritonavir and reverse transcriptase inhibitors is unlikely because of the different enzyme targets involved. One ZDV-resistant HIV-1 isolate tested in cell culture retained full susceptibility to ritonavir.

NONCLINICALTOXICOLOGY:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis:

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg per kg per day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 0.3-fold for males that of the exposure in humans with the recommended therapeutic dose (600 mg twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 0.6-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg per kg per day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 6% that of the exposure in humans with the recommended therapeutic dose. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known.

Mutagenesis

Ritonavir was found to be negative for mutagenic or clastogenic activity in a battery of *in-vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S.typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Impairment of Fertility

Ritonavir produced no effects on fertility in rats at drug exposures approximately 40% (male) and 60% (female) of that achieved with the proposed therapeutic dose. Higher dosages were not feasible due to hepatic toxicity.

4.2. POLYMER PROFILE

4.2.1.HYDROXY PROPYL METHYL CELLULOSE [53]

Chemical Name:

Cellulose 2- hydroxy propyl methyl ether

Nonproprietary Names **:** BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

Synonym:

Cellulose, Hypromellose, 2 – Hydroxypropylmethyl ether, Methyl hydroxy propyl cellulose, Methocel, Pharmacoat, Metolose.

Structure:

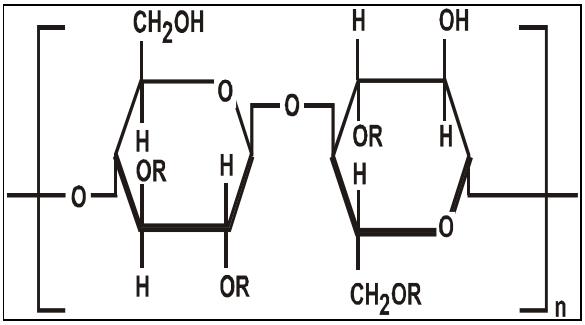


Figure 6.Hydroxypropyl methylcellulose

Chemical Name:

Cellulose 2- hydroxy propyl methyl ether

Mixed ether of cellulose with some of the hydroxyl groups in the form of methyl ether and some in the form of the 2-hydroxy propyl ether. Several grades of hydroxypropyl methylcellulose are distinguished by appending a number indicative of the apparent viscosity, in millipascal, of a 2% w/w solution measured at 20°C.

Hypromellose defined in the USP 25 specifies the substitution type by appending a four digit number to the nonproprietary name, e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of hydroxypropoxy group [OCH_2 CH C (OH) CH_3], calculated on a dried basis. Molecular weight is approximately 10,000 – 15, 00,000.

Description:

It is a white, yellowish white or greyish white, practically odorless, fibrous powder or granules.

Physical Properties

Solubility:

Soluble in cold water, forming a colloidal solution; practically insoluble in hot water, dehydrated alcohol, chloroform and ether.

P^H:

5.5 to 8.0.

Melting Point:

Browns at 190-200°C; chars at 225-230°C; Tg is at 170-180°C.

Bulk Density:

0.341 g/cm^3

Tapped Density:

0.557 g/cm^3

Enzyme Resistance:

Comparatively enzyme resistant

Gel Formation:

Undergoes a reversible transformation from solution to gel upon heating and cooling respectively.

Gel Point:

50 – 90°C depending upon the grade

Ash Value:

1.5 – 3 % depending upon the grade

Specific Gravity:

1.30

Surface Activity:

Provides some surfactant activity in solutions, surface tension for such solutions range from 42 – 56 dynes/cm.

Storage:

Store in well-closed containers.

Drug Excipients Interactions:

Hydroxy propyl methylcellulose is incompatible with some oxidizing agents.

Safety:

Hydroxy propyl methylcellulose is generally regarded as a nontoxic and nonirritant material although excessive oral consumption may have a laxative effect.

Pharmaceutical Uses:

HPMC is widely used in oral and topical pharmaceutical formulations. It is used as tablet binder, for film coating and in sustained release preparations. Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. It is also used as an emulsifier, suspending agent and stabilizing agent in topical gel and ointments.

4.3.EXCIPIENT PROFILE

4.3.1.SODIUM BICARBONATE[53]

Synonyms:

Baking soda; monosodium carbonate; sodium hydrogen carbonate; sodium acid carbonate

IUPAC Name:

Carbonic acid monosodium salt

Empirical Formula:

$NaHCO_3$

Molecular Weight:

84.01

Description:

Sodium bicarbonate occurs as an odourless, white, crystalline powder with saline, slightly alkaline taste.

Typical Properties:

Density (bulk):

0.869 g/cm^3

Density (tapped):

1.369g/cm^3

Melting point:

270°C

Pharmaceutical Application:

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain alkaline pH in preparation. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and tartaric acid combinations of citric and tartaric acid often preferred in formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone granules lose firmness. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin, lidocaine, local anaesthetic solutions. In some parenteral formulations (e.g. niacin), sodium bicarbonate is used to produce sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze drying stabilizer and in toothpastes.

Recently, sodium bicarbonate has been used as a gas forming agent in alginate raft systems and in floating, controlled release oral dosage forms of furosemide and cisapride. Therapeutically, sodium bicarbonate may be used as an antacid, and as the source of bicarbonate anion in a treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids.

Moisture content:

Below 80 % relative humidity, the moisture content is less than 1% w/w. above 85% relative humidity sodium bicarbonate rapidly absorbs water and may start to decompose with loss of carbon dioxide.

Incompabilities:

Sodium bicarbonate reacts with acids, acidic salt and many alkaloidal salts, with the evolution of carbon dioxide. In liquid mixtures containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of bismuth salt. In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine and levofloxacin.

4.4. MICROCRYSTALLINE CELLULOSE[53]

Nonproprietary Names:

BP : Microcrystalline Cellulose

JP : Microcrystalline Cellulose

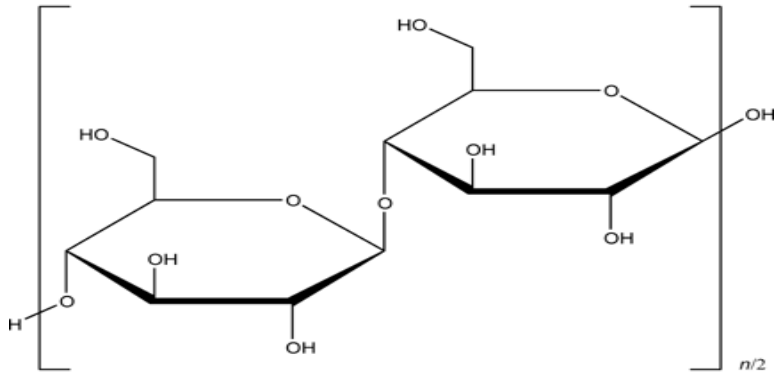
PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Synonyms:

Avicel PH; Cellets; Celex; cellulose gel; hellulosummicrocristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Structural Formula:



Chemical Name:

Cellulose [9004-34-6]

Formula and Molecular Weight:

$(C_6H_{10}O_5)n$,36 000

where n is 220.

Description:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

4.5. POLY VINYL PYRROLIDONE

(Grade used PVP K30)

Nonproprietary Names:

BP : Povidone.

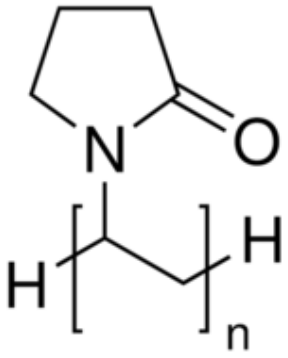
PhEur : Polyvidonum.

USP : Povidone.

Synonyms:

E 1201; Kollidon; Plasdone; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; Polyvinylpyrrolidone; PVP; 1-vinyl-2- pyrrolidinone polymer. .

Structural Formula:



Chemical Name:

1-Ethenyl-2- pyrrolidinone homo polymer

CAS Registry Number:

[9003-39-8]

Molecular Weight:

2500-3,000,000

Functional Category:

Suspending agent, tablet binder.

Description:

Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder .Povidones with K values equal to or lower than 30 are manufactured by spray drying and exist as spheres. Povidone K 90 having higher k value

povidones are manufactured by drum drying and exist as plates.

Stability and Storage Conditions:

Povidone darkens to some extent on heating at 150^0C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130^0C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry, place.

Pharmacopoeial Specifications

Test USP XXII

Identification+

pH 3.0 - 7.0

Water $\leq$ 5.0%

Residue on ignition $\leq$ 0.1%

Sulfated ash -

Lead $\leq$ 10ppm

Heavy Metals -

Vinylpyrrolidone $\leq$ 0.2%

K-value

≤ 15 85.0-115.0%

> 15 90.0-108.0%

Incompatibilities:

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins and other chemicals. It forms molecular adducts in solution with *sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin* and other compounds. The efficiency of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

Typical Properties:

Density: 1.17-1.18g/cm^3

Melting Point: Softens at 150^0C.

Solubility:

Freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons and mineral oil. In water the concentration of a solution is limited only by the viscosity of the resulting solution which is function of the K-value.

Safety:

Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site of intramascular injections formulated with povidone. Evidence also exists that povidone may accumulate in the organs of the body following intramascular injections.

Applications in Pharmaceutical Formulations:

Although povidone is used in a variety of pharmaceutical formulations it is primarily used in solid dosage form. In tableting, povidone solutions are used as binder in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol or hydroalcoholic solutions. Povidone solutions may also be used as coating agent.

Povidone is additionally used as a suspending, stabilizing or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

4.6.MAGNESIUM STEARATE[53]

Non-Proprietary Names:

BP: Magnesium stearate;

IP: Magnesium stearate

PhEur: Magnesiistearas;

USPNF: Magnesium stearate

Synonyms:

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula:

$C_{36}H_{70}MgO_4$

Molecular Weight:

591.34

The USP-NF describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

Structural Formula:

$[CH_3 (CH_2)_{16}COO]_2Mg$

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Physical Properties

Crystalline Forms:

High-purity magnesium stearate has been isolated as a trihydrate, a dehydrate and an anhydrate.

Density (bulk):

0.159 g/cm^3

Density (tapped):

0.286 g/cm^3

Density (true):

1.092 g/cm^3

Flash point:

250°C

Flowability:

Poorly flowing, cohesive powder.

Melting Range:

117–150°C (commercial samples); 126–130°C (high purity magnesium stearate).

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warmbenzene and warm ethanol (95%).

Specific Surface Area:

1.6–14.8 m^2/g

Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Pharmaceutical Application

Magnesium stearate is widely used in cosmetics, food and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

4.7.TALC[53]

Synonyms **:** Purified French Chalk, Purtalc, Soapstone.

Description **:** It is very fine, white to grayish-white colored odorless, impalpable, unctuous,crystalline powder.

Functional categories **:** Glidant and lubricant in tablets and capsules.

Solubility **:** Insoluble in water, organic solvent, dilute Acid & alkalis.

pH **:** 7.0 – 10.0 for a 20 % aqueous dispersion.

Loss on drying **:** < 1.0 %

Hygroscopicity **:** It absorbs insignificant amount of water at Relative humidities upto about 90 %.

Stability and storage

Conditions **:** It is a stable material. It should be stored in a Well-closed container in a cool, dry place.

Incompatibilities **:** Incompatible with quaternary ammoniuCompounds

Applications **:** It is widely used in oral solid dosage forms as a Lubricant & diluents. It is used as a dusting powder in topical use. Additionally used to clarify liquids and mainly used in food and cosmetics products because of its lubricant properties.

4.7. Preformulation studies

4.7.1.Determination of Melting Point.

Melting point of Ritonavir was determined by capillary method. Fine powder of Ritonavir was filled in glass capillary tube (previously sealed on one end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt by using the thermometer which was already immersed into the liquid paraffin in the apparatus.

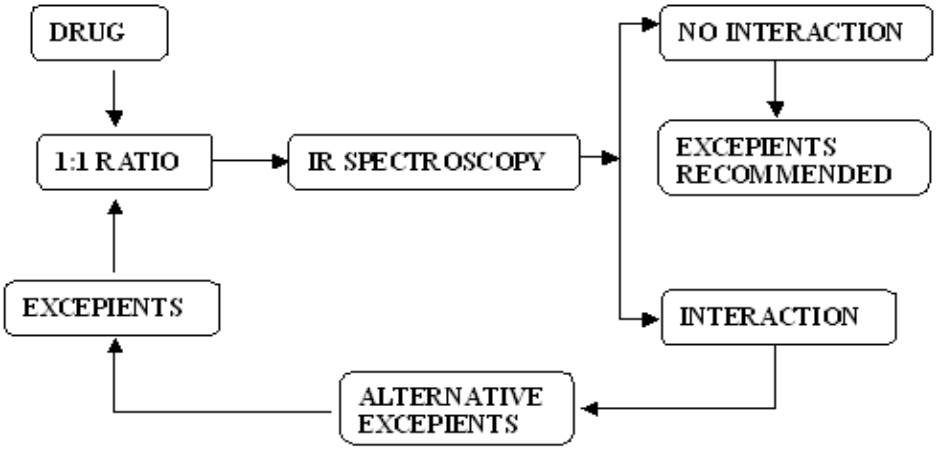
4.7.2.Compatibility study:

A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance.

4.7.3.FT-IR:

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis. Any changes in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

Schematic representation of compatibility studies



Procedure:

Weighed amount of drug (3mg) was mixed with 100mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.

4.7.4.Drug–Polymer Interaction/Compatibility study using FTIR

Fourier Transfer Infrared Spectroscopy

IR has been the method of choice to probe the nature and extent of interaction in polymer blends. IR was used in the study because mixing of the two components at molecular level will cause changes in oscillating dipoles of the molecules. If the drug and polymer interact then functional groups in FTIR spectra will show band shift and broadening compared to that of pure compounds.

Method

Potassium Bromide disc containing drug, polymer and their physical mixture were prepared to record the spectrum by using Shimadzu 8400S FTIR.

4.7.5.Standard Calibration Curve of Ritonavir

Ritonavir was quantitatively analyzed by various techniques. In the present study, Ritonavir was estimated by UV spectrophotometry method.

4.7.6. Determination of λ_{max} for Ritonavir

stock solutions of drug sample were prepared by dissolving 100.0 mg of drug in 100.0 ml of 0.1 N HCl were further diluted and analyzed spectrophotometrically to determine λ_{max}.

Observation:

The λ_{max} was found to be 246 nm.

Preparation of standard calibration curve of *Ritonavir* 0.1 N HCl

A. Preparation of 0.1 N HCl:

8.5 ml of conc. hydrochloric acid was diluted upto 1000 ml with distilled water, gives 0.1 N HCl.

B. Preparation of dilutions for standard curve:

Stock solution was prepared by dissolving 100.0 mg of *Ritonavir* in 100.0 ml of 0.1 N HCl solutions, which was further diluted to give the solutions of concentration 2, 4, 6, 8 and 10µg/ml respectively. Absorbance of these solutions were measured on UV spectrophotometer at 246 nm and plotted against the concentration to give the standard curve.

Table No. 7: Composition of Ritonavir Floating matrix Tablets

Slno	Composition of ritonavir	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Ritonavir	100	100	100	100	100	100	100	100	100	100
2	HPMC K4M	200	100	150	200	--	----	----	-----	-----	-----
3	HPMCK15M	----	-----	-----	------	100	150	200	-----	-----	------
4	HPMCK100M	----	-----	-----	------	-----	-------	------	100	150	200
5	SODIUM BICARBONATE	-----	30	30	30	30	30	30	30	30	30
6	MICROCRYSTALLINE CELLULOSE	80	150	100	50	150	100	50	150	100	50
7	PVPK30	10	10	10	10	10	10	10	10	10	10
8	MAGNESIUM STEARATE	5	5	5	5	5	5	5	5	5	5
9	TALC	5	5	5	5	5	5	5	5	5	5
	Total weight in mg	400	400	400	400	400	400	400	400	400	400

4.8.Formulation of Floating Tablets of Ritonavir by Direct compression technique

4.8.1.Preparation of Floating Tablets of Ritonavir

Technology Applied: Direct compression technique

The key ingredients included in the formulations are:

- Hydrophilic Polymers: HPMC K4M, HPMC K15M, HPMCK100M to modify the pattern of drug release from matrix.
- Effervescent agent: Sodium bicarbonate
- Filler: Micro Crystalline Cellulose
- Antiadherant: Talc
- Lubricant: Magnesium Stearate.

Procedure:

Floating tablets of each containing 100mg ritonavir drug were prepared by direct compression technique.The composition of various formulations of the tablets with their codes were listed in the table. Accurately weighed quantities of polymer and MCC for each batch were taken in a mortar and mixed geometrically, to this required quantity of Ritonavir was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate, citric acid was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the ritonavir blend which was also passed through sieve no 40. The whole mixture was mixed for 3 minutes. To this Magnesium stearate was added and mixed for minutes, later Talc was added and mixed for 2 minutes. The composition of various formulations was given in above table.7

4.9.Evaluation of powder characteristics

Pre-Compression Parameters:

Angle of Repose

Angle of response is the angle of inclination, formed to the flat surface by the bulk of granules when it is allowed to flow under gravitational force from a fixed height. It is a characteristic of granule flow properties and is calculated by using the formula.

$$\theta = \tan^{-1} (h/r)$$

Where

θ - Angle of repose

h - Height of granule above flat surface

r - Radius of circle formed by the granule pile

Bulk Density:

The bulk density was determined by pouring perceived drug excepient blend into a graduated cylinder and measuring the volume and weight. It is expressed in g/ml and is given by

$$D_b = M/V_o$$

Where

M is the mass of powder

Vo is the bulk volume of powder

Tapped density:

It was determined by placing a graduated cylinder containing a known mass of drug excipients blend, on mechanical tapping apparatus.The tapped volume was measured by tapping the powder to constant volume is expressed in g/ml. and is given by

$$Dt = M/Vt$$

Carr's Compressibility Index

It is also a characteristic of granule flow properties. The bulk density and tapped density was measured and compressibility index was calculated using the formula,

$$C.I. = \{ (P_t - P_0) / P_t \} \times 100$$

Where, P_t = tapped density

P_0 = bulk density

Hausner's Ratio

Tapped density and bulk density were measured and the hausner ratio was calculated using the formula,

$$\text{Hausner ratio} = P_t / P_0$$

Where, P_t = tapped density

P_0 = bulk density

Determination of Drug Content :

Twenty tablets were taken ,powdered and the powder equivalent to one dose each was transferred to a 100 ml of volumetric flask and 0.1N Hcl was added .The volume was then made up to the mark with 0.1N HCl .The solution was filtered and diluted and the samples was estimated by using U V.Visible Spectro photometer at lamda max of 276nm.

Post-Compression Parameters:

4.10.Evaluation of Tablets

Hardness test

Tablet hardness has been defined as the force required for breaking a tablet in a diametric compression test. A tablet was placed between two anvils of the hardness tester (Monsanto type), force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded.

Friability test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. Preweighed tablet samples (20 tablets) were placed in the friabilator, which was then operated for 100 revolutions, dropping the tablets a distance of 6 inches with each revolution. The percentage friability was calculated using the formula.

$$\% \text{ friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \text{x} 100$$

Weight variation test

20 tablets were selected at random and weighted individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablets weighed over 100 mg, I.P. specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 5%.

Determination of Drug content

To evaluate tablets potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet, and batch to batch. To perform the test, ten tablets from each batch were weighed and powdered. Powder equivalent to the

average weigh of the tablet was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of distilled water. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV spectrophotometer at 246nm.

***In-vitro* buoyancy Study:**

The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) and duration of time by which the dosage form constantly emerge on surface of medium called total floating time.(TFT).

Procedure

The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid,pH 1.2 as per USP.The temperature of medium was maintained at 37±2 ^{o}C. the time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium was noted.

At initial time **After 5min**

Fig. 12: Floating behavior of Ritonavir Floating Tablet (F7)

4.11.Water Uptake Studies:

Study of Swelling behaviour

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet.

***In-vitro* Dissolution Study**:

Dissolution of the tablet of each batch was carried out using USP type I apparatus (Basket type).

Procedure

Nine 100 ml of 0.1 N HCl was filled in a dissolution vessel and the temperature of the medium was set at 37±2^{o}C. Tablet was placed in each dissolution vessel and rotational speed of basket was set at 50 rpm. The 5 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1 N HCl as blank at λ_{max} of 246 nm using double beam UV visible spectrophotometer. The content of drug was calculated using the equation generated from standard curve. The % cumulative drug release was calculated.

4.12 Study of drug release kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage from is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation. The results are given in Table 26.

Zero Order Release Kinetics:

It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_o t$$

Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from

most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\text{In } (1\text{-}Q) = -\ K_1 t$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi's equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=K_2 t^{½}$$

Where,

K_2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Power Law:

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsemeyer equation (Power Law).

$$M_t/M_\alpha = K.t^n$$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the $M_t/M_\alpha$is the fraction of drug released at time t,k is the kinetic

constant and n is the diffusional exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table-6. A plot between log of M_t/M_α against log of time will be linear if the release obeys Peppas and Korsemeyer equation and the slope of this plot represents "n" value.

Table 8: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

4.13. Stability Studies:[29]

Introduction

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. In addition, product-related factors influence the stability, e.g. the chemical and physical properties of the active substance and the pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system, and the properties of the packaging materials. Also, the stability of excipients that may contain or form reactive degradation products, have to be considered.

Table- 9: Objectives of Stability Testing:

OBJECTIVE	TYPE OF STUDY	USE
To select adequate (from the viewpoint of stability) formulations and container-closure systems	Accelerated	Development of the product
To determine shelf-life and storage conditions	Accelerated and real-time	Development of the product and of the registration dossier
To substantiate the claimed shelf-life	Real-time	Registration dossier
To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product	Accelerated and real- time	Quality assurance in general, including quality control.

Climatic Zones and Conditions

WHO has issued guidelines, where it is stated that the world is divided into four zones based on the prevailing annual climatic conditions for the purpose of stability testing.

Zone I: temperate

Zone II: subtropical with possible high humidity

Zone III: hot/dry

Zone IV: hot/humid

Table-10: Mean climatic conditions: measured data in the open air and in the storage room

Climatic Zone	Measured data in the Open Air		Measured data in storage room	
	^{o}C	**%RH**	**^{o}C**	**%RH**
I	10.9	75	18.7	45
II	17.0	70	21.1	52
III	24.4	39	26.0	54
IV	26.5	77	28.4	70

So for example if a manufacturer plans to sell his products in zone-III he/she should do real time studies at 30^{o}C and 35%RH.If a manufacturer wants to apply for the registration of a new drug, i.e. if he is applying for a (1) Investigative New Drug Application (IND) or (2) New Drug Application (NDA) or (3) Abbreviated New Drug Application (ANDA) then he has to assure the FDA regarding the drug's/drug product's safety, quality and efficacy. For this he has to carry out stability tests and submit stability data. How he should do this is specified by Q1A (R2).

Selection of Batches

Data from formal stability studies should be provided on at least three primary batches of the drug substance. These batches should be made to a minimum of pilot scale by the same synthetic route as that of the production batches.

Specifications which include testing methods and acceptance criteria should be fixed.

Testing frequency in Months

Long term: 0, 3, 6, 9, 12, 18, 24

Accelerated storage: 0, 3, 6

Storage conditions recommended

Table-11 : Testing frequency for different storage conditions

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long term*	$25^0C + 2^0C/60\%$ RH + 5% RH or $30^0C + 2^0C/65\%$ RH + 5% RH	12 months
Intermediate**	$30^0C + 2^0C/65\%$ RH + 5% RH	6 months
Accelerated	$40^0C + 2^0C/75\%$ RH + 5% RH	6 months

* It is up to the applicant to decide whether long term stability studies are performed at 25 + 2^oC/60% RH + 5% RH or 30 ^0C + 2^oC/65% RH + 5% RH.

** If 30^oC + 2^oC/65% RH + 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25^oC+ 2^oC/60% RH + 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria (ICH, 2003)

"Significant change" for a drug substance is defined as failure to meet is specification.

Table -12 : Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	$5^0C + 3^0C$	12 months
Accelerated	$25^0C + 2^0C$/60% RH + 5% RH	6 months

Table-13 : Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	$20^0C + 5^0C$	12 months

Stability Testing for Established Drug Substances:

WHO has issued guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage form. The stability of finished pharmaceutical products depends on environmental factors and on product related factors. So stability considerations should be given, the highest priority in the design and formulation of a product. The shelf life should be established with due regard to the climatic zones. To ensure both patient safety and the rational management of drug supplies, it is important that the expiry date and storage conditions are properly indicated on the label.

Accelerated stability testing:

These are the studies designed to increase the rate of chemical degradation and physical change of a drug by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from real – time stability studies, may be used to assess longer – term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes. These are also known as stress testing studies.

Expiry date:

The date given on the individual container of a drug product up to and including which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life period to the date of manufacture.

Real time (Long term) stability studies:

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of a drug, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the shelf life, to confirm the projected shelf life and to recommend storage conditions.

Stability tests:

A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage conditions.

5. RESULTS AND DISCUSSION

5.1 Preformulation study:

5.1.1. Organoleptic Properties:

Organoleptic Properties for Ritronavir was done as per IP specification and the result was given in the below table.14

Table.14: Study of Organoleptic properties of Ritronavir

Test	Specification of IP	Results
Character	white-to-light-tan powder	White hygroscopic powder

5.1.2. Solubility:

Solubility test for Ritronavir was done as per IP specification and the result was given in the below table.15

Table.15: Study of Solubility properties of Ritronavir

Test	Specification of IP	Results
Solubility	It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.	Soluble in Alcohol, Ethanol, Methanol and Sparingly soluble in water.

5.1.3. Melting point:

Melting point for Ritronavir was done as per IP specification and the result was given in the below table.17

Table.17: Study of Melting point properties of Ritronavir

Test	Specification of IP	Results
Melting Point	120^0C – 122^0C	121.2^0C

Discussion:

Preformulation studies indicate that the drug Ritonavir passes the identification test specified in IP. The physical parameters of drug as well as excipients concluded that these were considerably good to formulate the tablet by direct compression technique.

5.1.4. IR spectra:

IR spectra for Ritronavir was done as per IP specification and the result was given in the below table.16

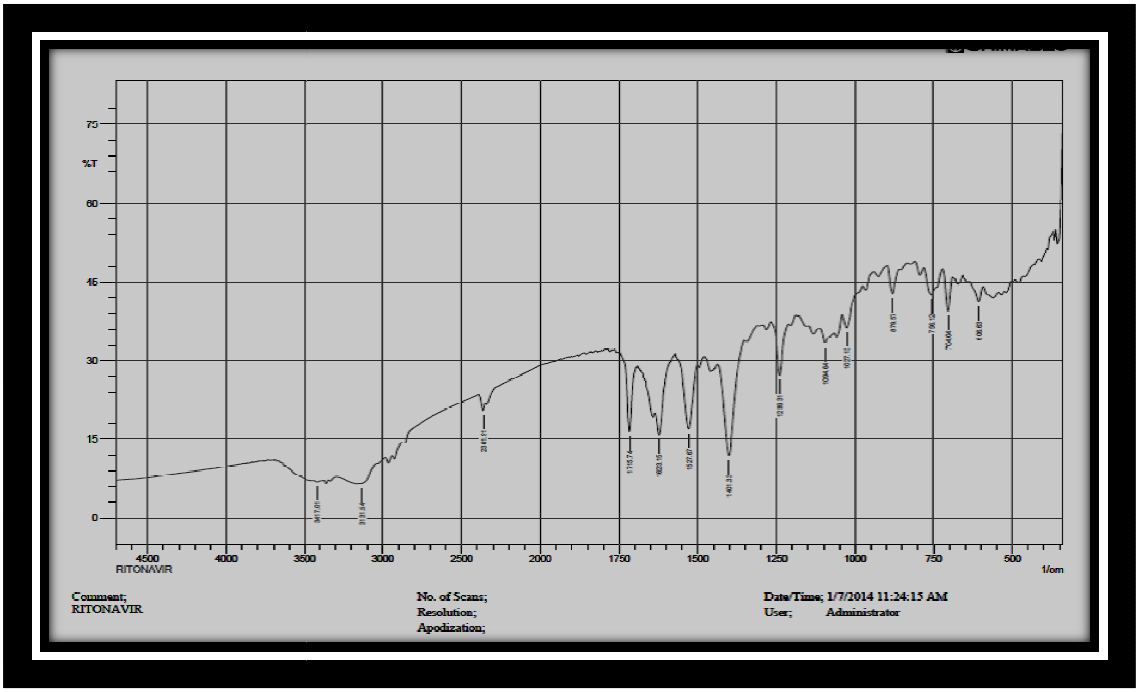
Table.16. Study of IR spectra properties of Ritronavir:

Test	Specification of IP	Results
IR Spectra	The potassium bromide disc contain drug was prepared to record the spectrum by using FTIR spectrophotometer	The spectrum showed all prominent peaks of Ritonavir

5.1.5. Drug–Polymer Interaction/Compatibility study using FTIR

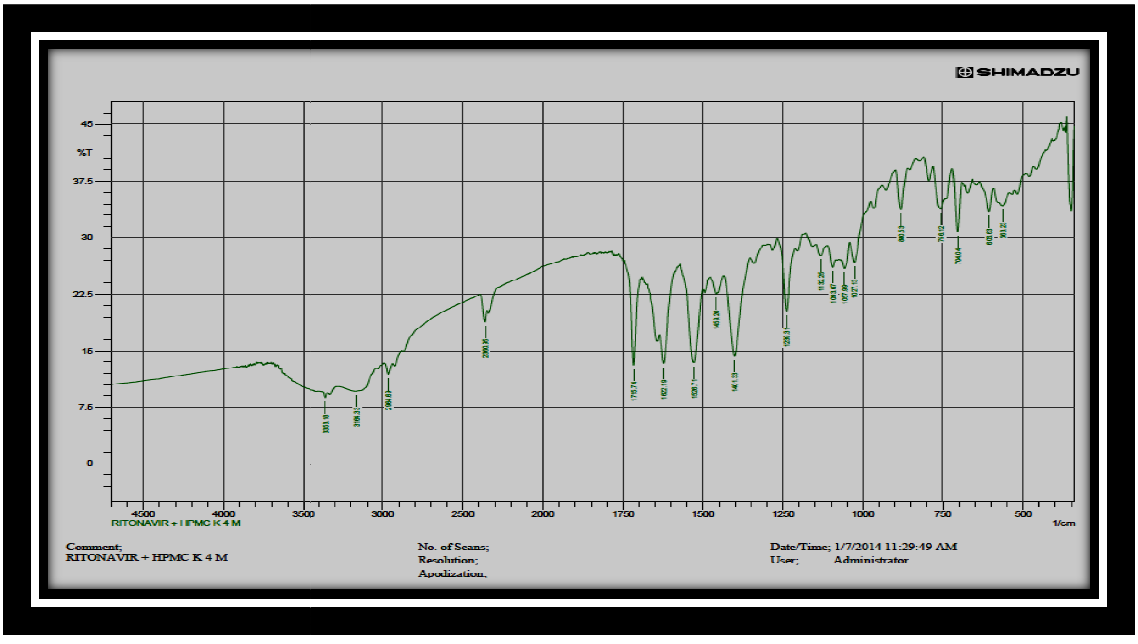
The FTIR spectra of the pure drug showed significant bands atcm3131, 3417, 2301, 1715, 1527cm^{-1} which indicates the presence of hydroxyl, ether stretching, tertiary amine salt, carbonyl groups and phenyl nucleus skeletal stretching respectively. The different peaks of drug, polymer and their physical mixture indicate all groups and characteristics of the drug were not altered. There is no significant interaction in drug and polymer.

Graph No.1: FTIR Spectral Analysis of Ritonavir



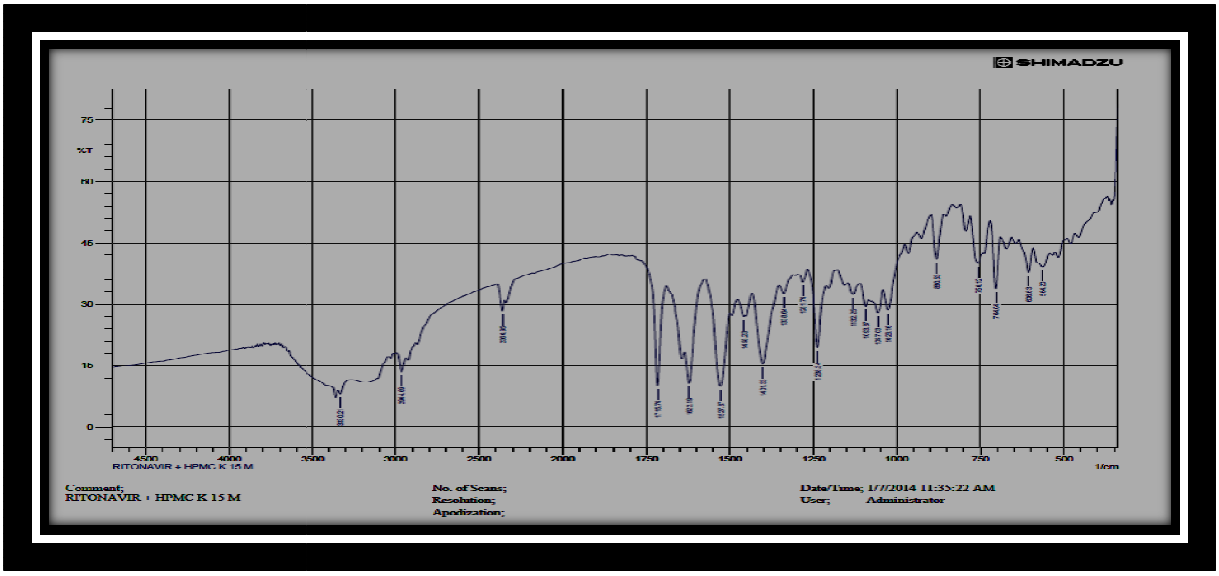
Graph No.2: FTIR spectral analysis of Physical mixture of Drug and polymer

(Ritonavir +HPMC K4M)



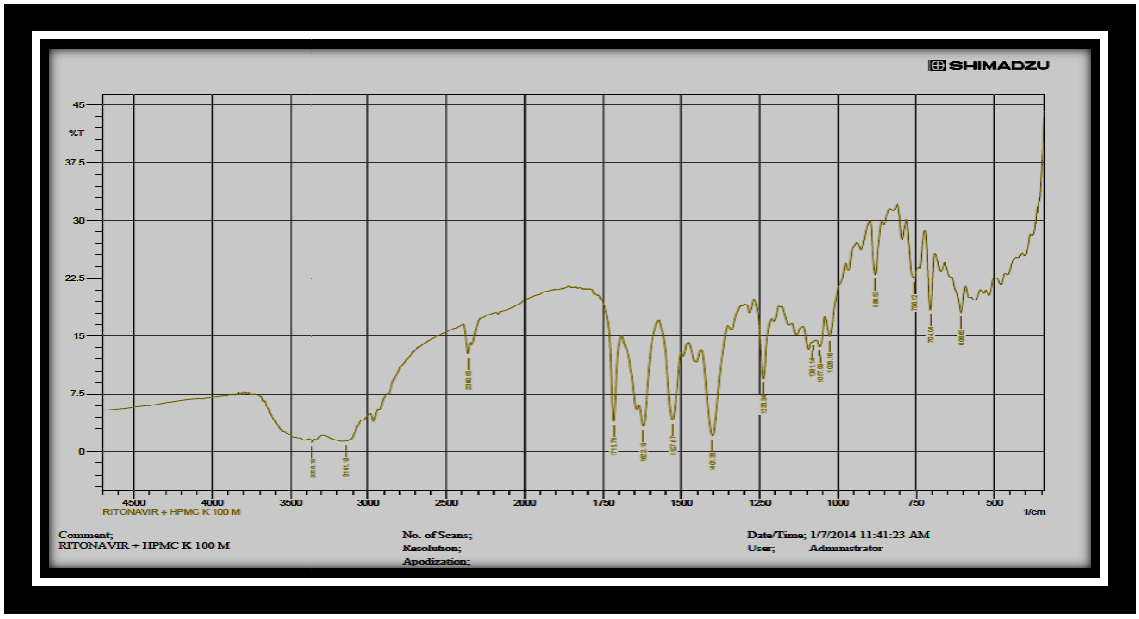
Graph No.3: FTIR spectral analysis of Physical mixture of Drug and polymer

(Ritonavir +HPMC K15M)

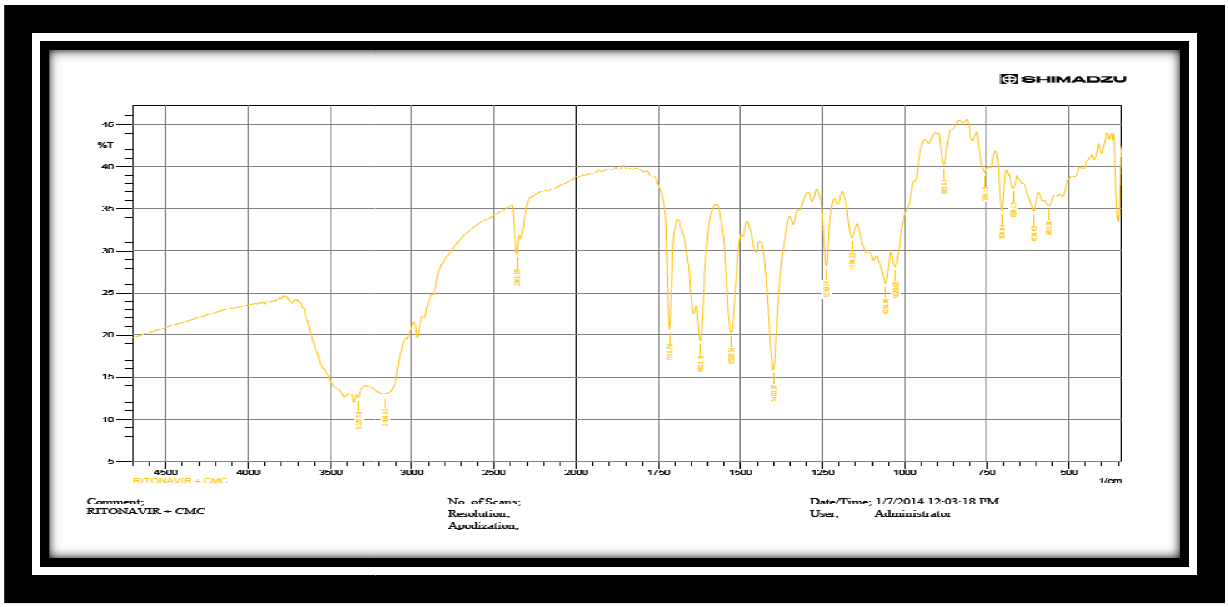


Graph No.4: FTIR spectral analysis of Physical mixture of Drug and polymer

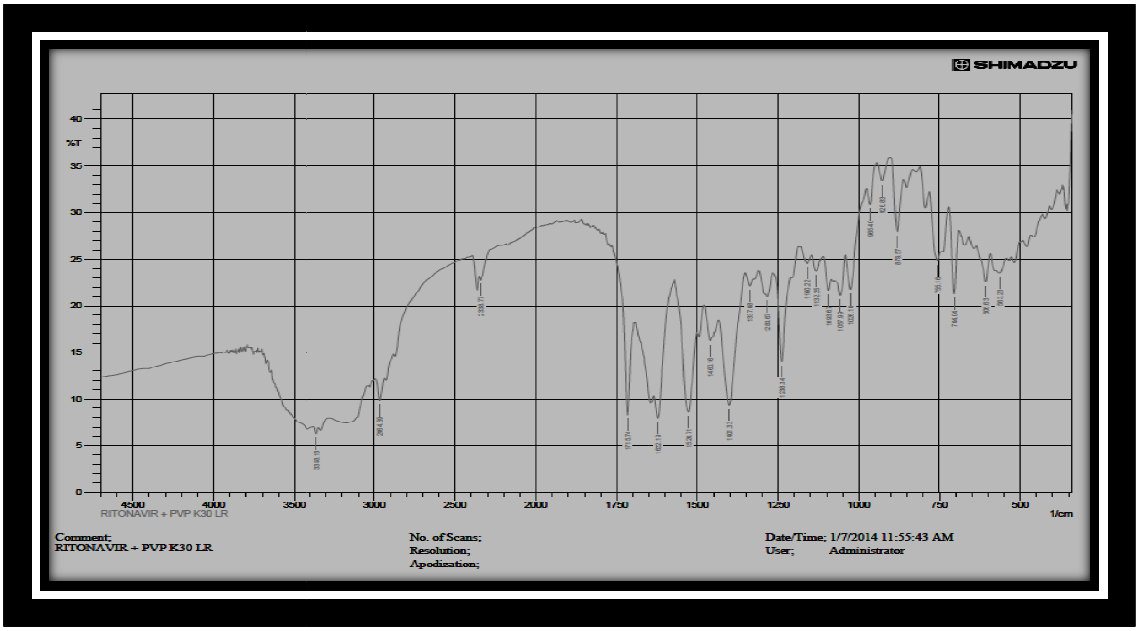
(Ritonavir + HPMCK100M)



Graph No.5: FTIR spectral analysis of Physical mixture of Drug and polymer (Ritonavir +Microcrystalline cellulose)



***Graph No*.6: FTIR spectral analysis of Physical mixture of Drug and polymer (Ritonavir + PVP K30)**



Discussion:

Physical mixture of drug and polymer was characterized by FTIR spectral analysis (Graph 1, 2, 3, 4, 5 and 6) for any physical as well as chemical alteration of drug characteristics. From results, it was concluded that there was no interference in the functional group as the principle peaks of Ritonavir were found to be unaltered in the drug polymer physical mixture.

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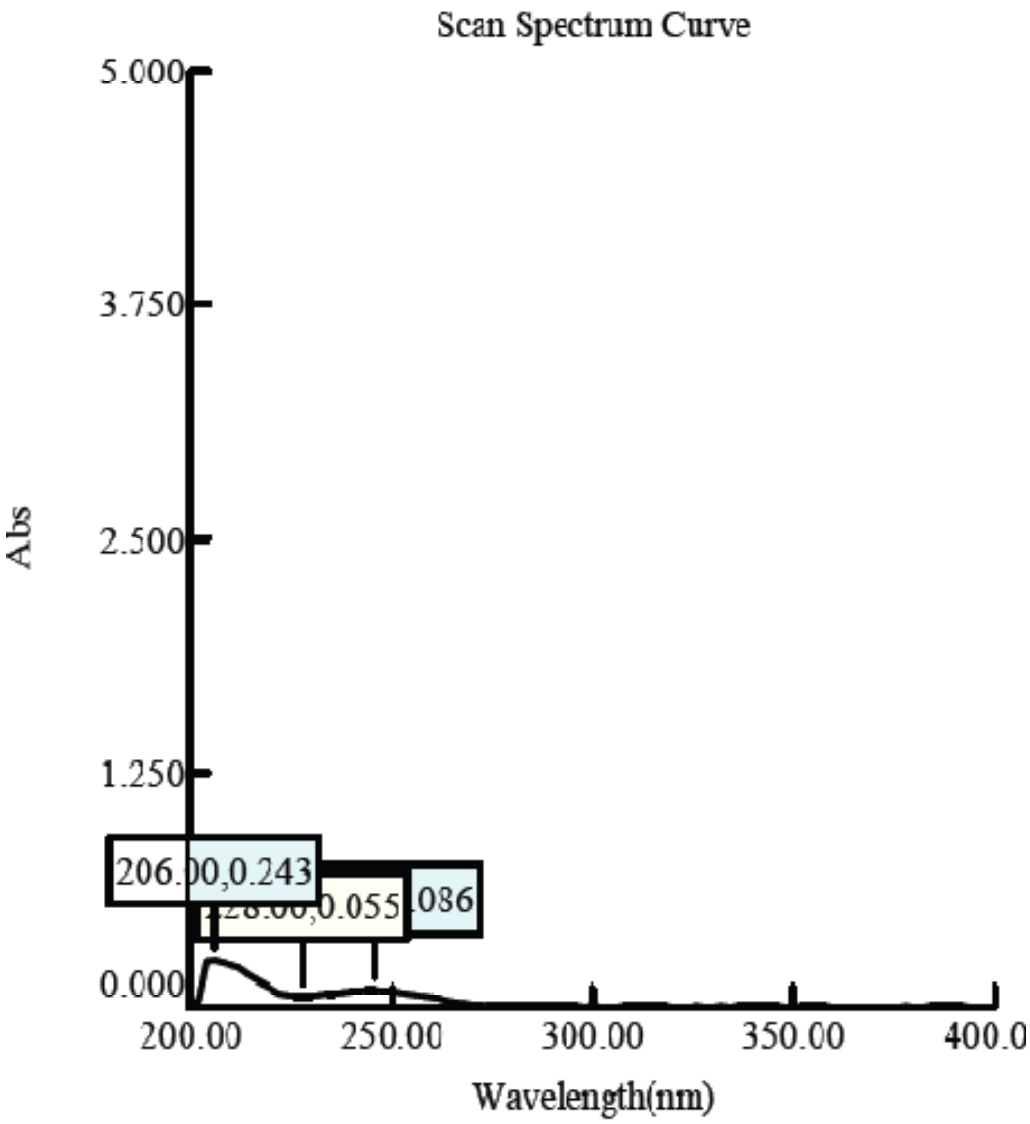


Graph 7: Lambda max of Ritonavir

Instrument Performance

Model : UV-VIS Spectrophotometer

Number : 19-1885-01-0126

Spectral Bandwidth : 2.00 nm

Scan Spectrum Performance

Scan Range : 200.00 to 400.00 nm

Measure Mode : Abs

Interval : 2.00 nm

Speed : Fast

Data File : Untitled1.spd

Create Date/Time : Friday, January 24, 2014 4:05:09 PM

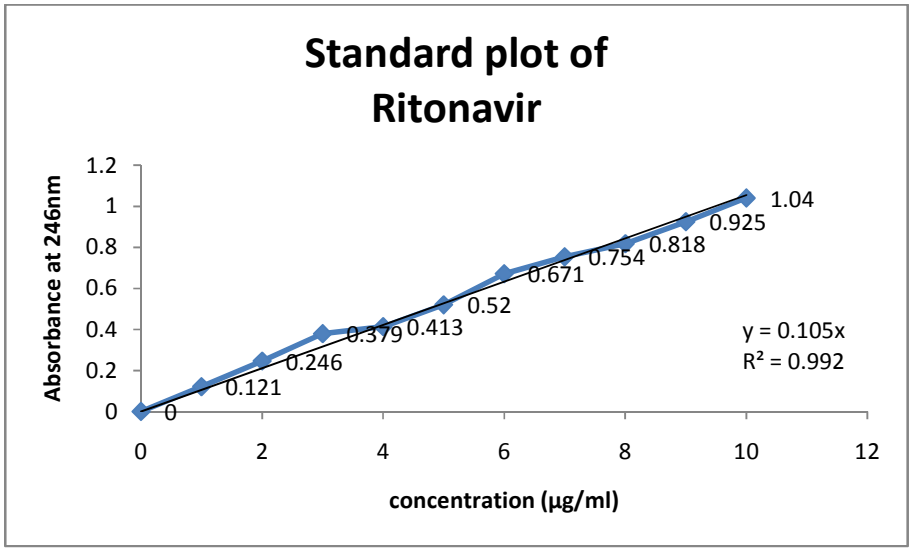
Data Type : Original

Method File:

No.	P/V	Wavelength(nm)	Abs	Comment
1	Peak	246.00	0.086	
2	Peak	206.00	0.243	
1	Valley	228.00	0.055	

5.2. Standard Calibration Curve of Ritonavir

Graph 8: Calibration curve of Ritonavir 0.1 N HCl



Discussion:

From the scanning of drug in 0.1 N HCl, it was concluded that the drug had λ_{max} of 246.0 nm and which was exactly similar as reported. From the standard curve of 0.1 N HCl it was observed that the drug obeys Beer – Lambert's law in concentration range of 2 – 12µg / ml in the medium.

5.3. Pre formulation studies:

Table No. 18: Study of Characteristics of Final blend

Formulations	Angle of repose (θ)	Bulk density	Tapped density	Compressibility Index or Carr's Index (%)	Hausner's ratio
F_1	$17^0.10'$	0.372	0.400	7	1.075
F_2	$21^0.40'$	0.345	0.388	11	1.124
F_3	$19^0.20'$	0.311	0.360	13.6	1.157
F_4	$17^0.30'$	0.266	0.302	11.9	1.135
F_5	$20^0.70'$	0.223	0.258	13.5	1.156
F_6	$18^0.30'$	0.274	0.320	14.3	1.167
F_7	$21^0.20'$	0.341	0.374	8.82	1.096
F_8	$20^0.10'$	0.277	0.320	13.4	1.155
F9	$22^0.50'$	0.270	0.320	14.62	1.185
F10	$22^0.10'$	0.279	0.321	15.58	1.150

Discussion:

Table.18 indicates the powder characteristics of various batches of floating tablets. Various formulations show good flow properties. Results of Angle of repose ($17^0.10' – 22^0.50'$), Bulk density (0.223-0.372), Tapped density (0.258-0.400), Carr's

index (7 – 15.58) and Hausner's ratio (1.075-1.185) shows satisfactory results, which is required for better bioavailability.

5.4. Physical Properties

Table No. 19: Physical Properties of each Batch of Ritonavir Floating matrix Tablets

Batch code	Weight variation (mg)	Hardness(kg/cm^2)	Friability (%)	Drug uniformity (%)
F1	396±5	16.0	0.285	99.09
F2	394±5	16.3	0.223	97.18
F3	394±5	16.2	0.286	99.29
F4	394±5	17.2	0.230	96.10
F5	395±5	16.8	0.231	97.26
F6	393±5	16.5	0.239	98.81
F7	395±5	16.2	0.291	99.96
F8	398±2	16.4	0.228	97.49
F9	393±5	16.3	0.229	97.56
F10	393±5	16.8	0.291	98.99

Discussion:

From the physical parameters (Table 19) of each batch, it was concluded that the tablets of all batches had desirable physical characteristics. Results of Hardness of various batches of prepared formulations (16.0 –17.2kg / sq cm.) and Friability (0.223 – 0.291 %) indicates that the tablets having sufficient strength to withstand physical

abrasion. Tablets of all batches pass the weight variation test as per the limits prescribed in IP. (5% deviation is allowed for average weight of tablet X ≥ 250 mg).

5.4.1. *In-vitro* Buoyancy study:

Table 20: *In-vitro* Buoyancy study of Ritonavir Floating Tablets

Batch Code	Floating Lag Time(sec)	Total Floating Time (Hours)
F1	Did not float	Did not float
F2	14	>5
F3	17	>7
F4	24	>9
F5	16	>12
F6	21	>12
F7	14	>12
F8	10	>12
F9	12	>12
F10	17	>12

Discussion:

The Initial batch is prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas generating agent in order to float the tablet. The sodium bicarbonate induces Co_2 generation in the presence of dissolution medium (0.1N Hcl). The gas generated is trapped and

protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1gm/ml, and the tablet become buoyant. To study the effect of sodium bicarbonate concentration on floating lag time batches F1 to F10 were selected. Sodium bicarbonate 30 mg was essential to achieve optimum *in-vitro* buoyancy (i.e floating lag time of 14-24 seconds and floating duration of 12 hrs). It was observed that floating lag time for this system in the range of 14 to 24 sec's and flotation was achieved maximum at gas generating quantity of 30 mg with in 14 min. as shown in the table 20.

5.4.2. Water Uptake Studies

Table No. 21: Study of swelling characteristics of floating tablets of Ritonavir

Batch Code	Time in hrs. (% Swelling)			
	2	4	6	8
F1	56.75	83.70	72.98	74.06
F2	46.85	90.88	67.43	66.23
F3	64.47	74.63	70.38	72.01
F4	63.98	67.74	76.41	63.59
F5	90.61	122.12	84.70	70.67
F6	57.84	72.25	71.10	60.65
F7	54.87	72.21	69.34	64.04
F8	53.57	66.79	65.5	60.63
F9	62.79	94.94	86.50	80.43
F10	59.13	67.40	81.15	80

Discussion:

Water uptake (swelling) study, Table No.21 cleared that order of swelling observed in these polymers could indicate the rates at which the preparations are able to absorb water and swell. Maximum liquid uptake and swelling of polymers were achieved after 4-8 hrs. The swelling index was calculated with respect to time. As the time increases, the swelling index was increased, because weight gain by the tablet

was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outer most gelled layer of tablet into dissolution medium.

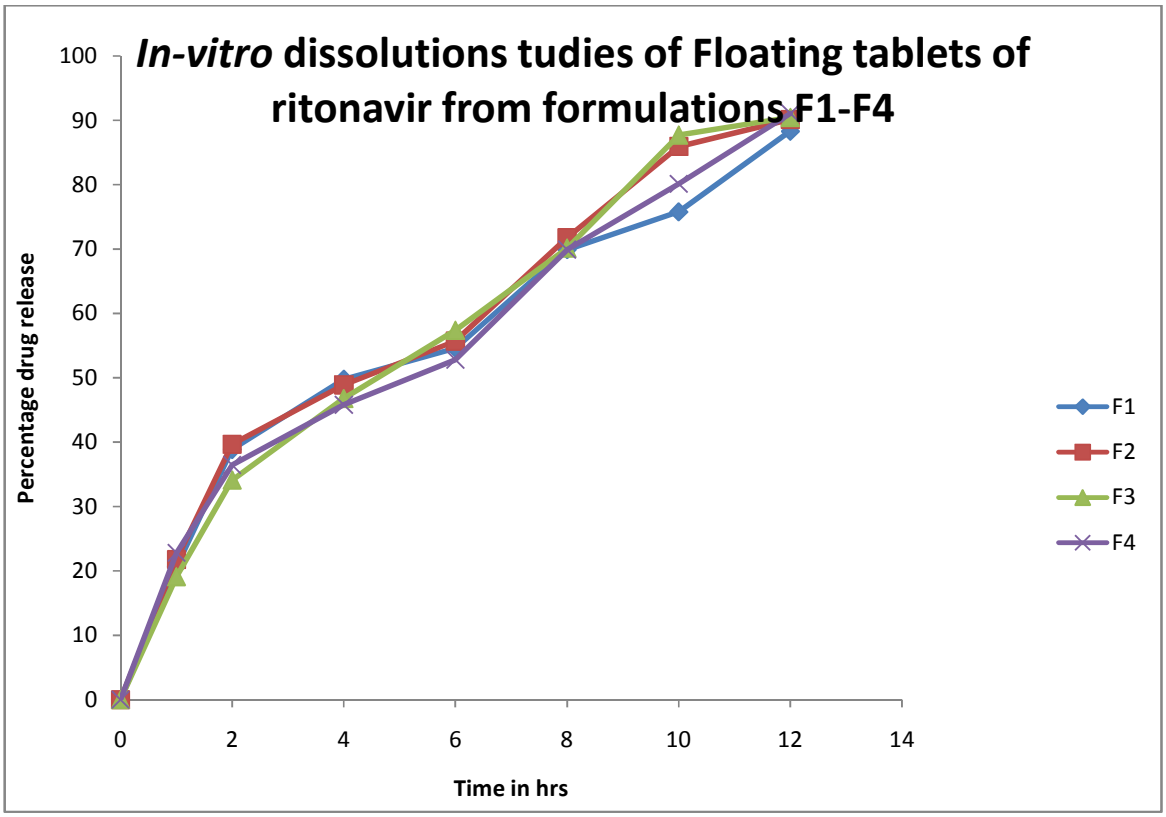
5.4.3. *In-Vitro* Dissolution Study

Table No. 22: *In-Vitro* Dissolution Data of Floating Tablet of ritonavir

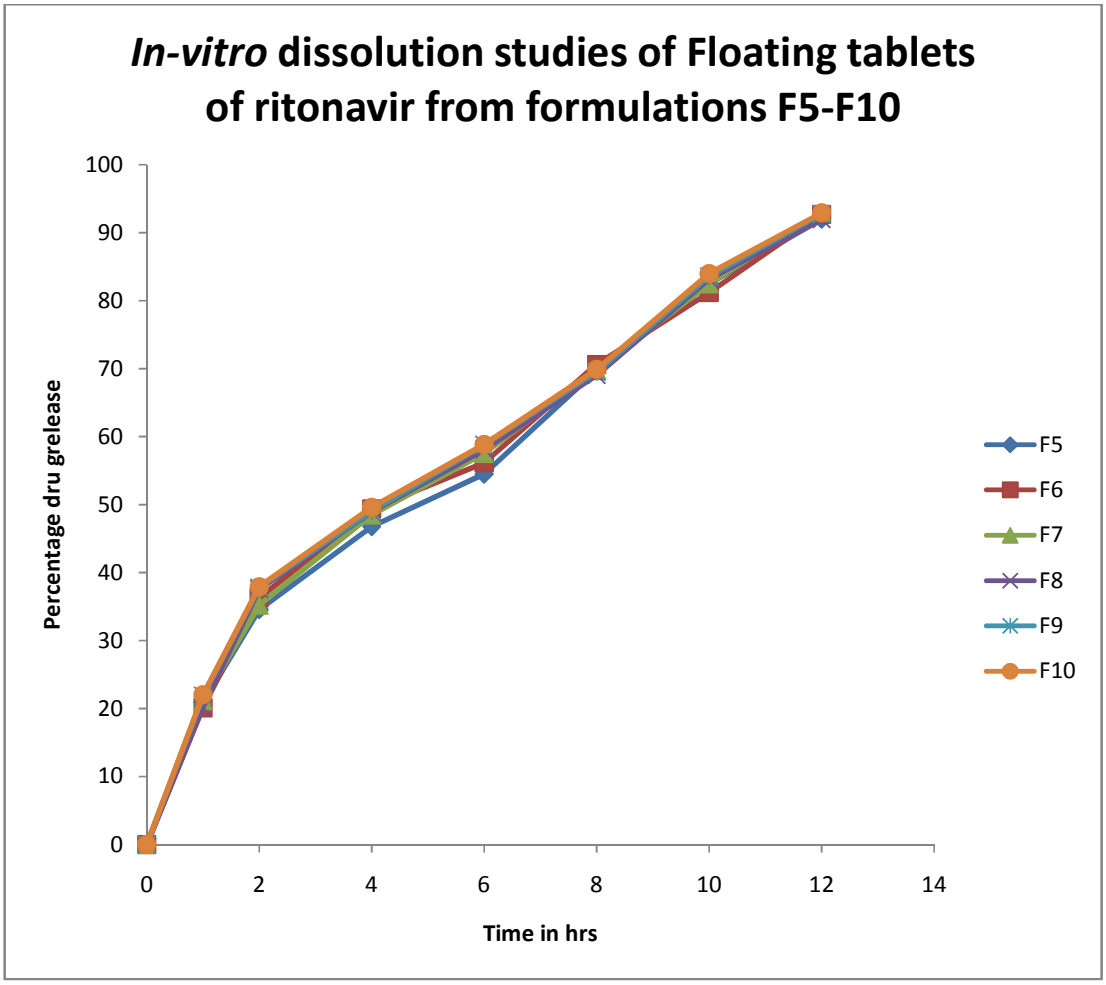
S.NO	TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	1	20.67	21.78	19.10	22.79	20.89	20.10	21.11	20.15	21.90	22.02
2	2	38.85	39.67	34.12	36.45	34.56	36.29	35.21	37.56	37.78	37.89
3	4	49.76	48.89	46.76	45.80	46.78	49.38	48.49	48.94	49.09	49.59
4	6	54.58	55.69	57.37	52.79	54.50	56.12	57.50	58.10	58.78	58.81
5	8	69.89	71.76	70.15	69.90	69.78	70.59	69.71	69.07	69.56	69.89
6	10	75.76	85.91	87.71	80.15	82.51	81.19	82.45	83.19	83.57	83.96
7	12	88.29	90.12	90.45	91.07	91.99	92.67	92.94	91.96	92.74	92.89

5.4.3. *In-Vitro* Dissolution Studies

Graph No. 9: *In-Vitro* Dissolution Profile of F1-F4)



Graph No. 10: *In-Vitro* Dissolution Profile of F5-F10



Discussion:

Table 23, indicates the dissolution data of various batches of floating tablets. The percentage drug release from batch F1 to F10 vary from 88.29 to 92.94%. In formulations F2 to F4 HPMC K4M were showed 91.07%, 91.99%, 92.67% at the end 12th hour and formulations. From F5 to F7 (HPMC K15M) were showed the results as 91.99%, 92.67%, 92.94 and from formulations F8 to F10 (HPMC K100M) shows the results 91.96%, 92.74% and 92.89%.Incomparison of F7 & F10, F7 shows highest percentage drug release i.e. with HPMC K15M. Formulation F7 is selected as optimized formulation among all the formulations F7 is showing 92.94 % sustained

release at the end of 12 hours as shown in graph 10. Formulation F7 is selected as optimized formulation because of using hydrophilic polymer HPMC K15M Among all formulations K15M grade provided better controlled release characteristics with excellent drug release and *in-vitro* buoyancy. From the above results, it was also evident that at higher viscosity grades of polymer concentrations, the rate of drug release was retarded greatly.

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5.5. Study of drug release kinetics:

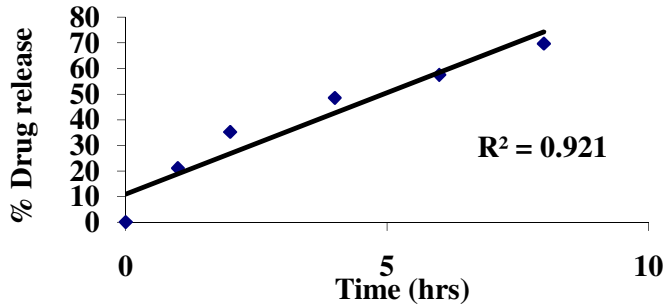
Table No. 23: Dissolution Kinetics of Formulation F7 Ritonavir Floating Tablets

Formulation Code	Zero order	First order	Higuchi	Korsemeyer-Peppas		Best fit Model
	R	R	R	R	N	
F1	0.889	0.954	0.970	0.955	0.652	**Higuchi**
F2	0.895	0.962	0.963	0.997	0.850	**peppas**
F3	0.938	0.957	0.978	0.989	0.824	**peppas**
F4	0.905	0.939	0.970	0.984	0.824	**peppas**
F5	0.925	0.943	0.981	0.998	0.814	**peppas**
F6	0.915	0.934	0.985	0.995	0.726	**peppas**
F7	0.921	0.935	0.990	0.998	0.703	**peppas**
F8	0.906	0.948	0.982	0.991	0.697	**peppas**
F9	0.904	0.941	0.985	0.990	0.684	**peppas**
F10	0.903	0.941	0.984	0.991	0.692	**peppas**

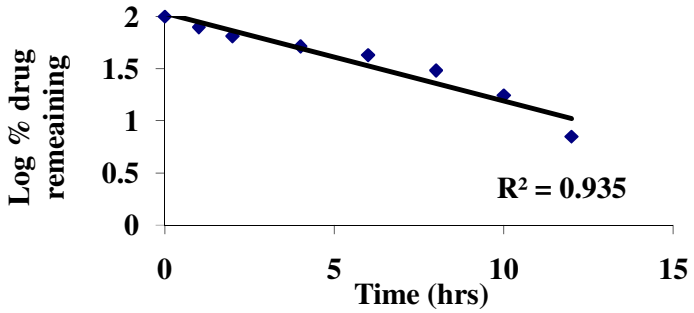
Discussion:

Table 23 indicates the release kinetics of floating tablets of Ritonavir. Dissolution data of batch F_7 were subjected to treatment with different kinetics equations, which showed the release patterns.

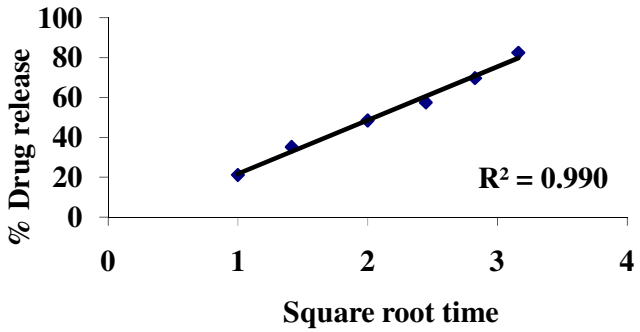
Graph No. 11: Zero Order Plot



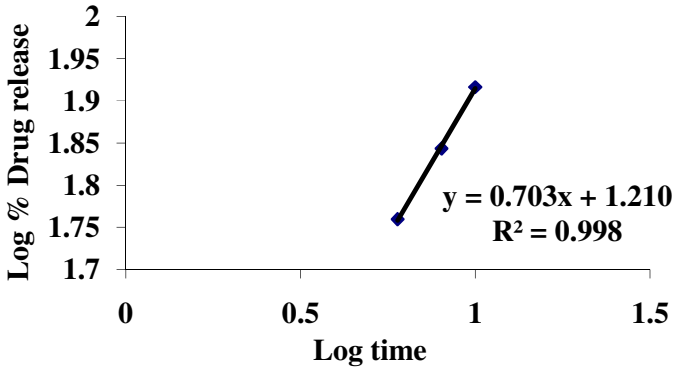
Graph No. 12: First Order Plot



Graph No. 13: Higuchi's Plot



Graph No: 14 Peppas Koresmeyer's plot



Discussion:

Regression co-efficient value (R^2) and n values for all formulation were shown in table 24. The release profile of the optimized formula F7 fitted best to Korsemeyer's plot with R^2 value of 0.999. As the n value for the Korsmeyer-Peppas model was found to be less than 0.698, it follows non fickian transport.

5.6 Determination of stability study of an optimised formulation:

Table.24. Stability studies of ritonavir floating tablets.

Parameters	After 15 days	After 30 days	After 45 days
Physical appearance	No change	No change	No change
Weight variation (mg)	395±1.6	395±2.70	395±1.30
Hardness (kg/cm^2)	16.2±0.23	16.32±0.64	16.32±0.99
Friability (%)	0.291±0.05	0.291±0.08	0.30±0.06
Drug content (mg/Tab)	99.91±0.34	98.99±0.29	98.90±0.87
Buoyancy lag time (sec)	14±1.60	14±2.8	14±3.10
Duration of Buoyancy (Hours)	>12	>12	>12

Discussion:

According to ICH guidelines, 45 days stability study at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% of optimized formulation (F7) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at 4^0C ±2^0C, 27^0C ±2^0C and 45^0C ±2^0C for 45 days at RH 75±5% for 45 days.

6. SUMMARY& CONCLUSION

In the present work attempts have been made to formulate floating tablets of Ritonavir with HPMC K4M, HPMC K15M, HPMC100M, by direct compression method by taking single polymer in the formulation. Ritonavir has shown high solubility in 0.1 HCl, therefore it was considered as a good candidate for gastro retentive dosage form

Ritonavir is used for the treatment of HIV which has a short elimination half-life of 3-5 hours. Its dose is 100 to 400 mg/day orally in 1 or 2 divided doses. Because of frequent administration and short elimination half-life, Ritonavir is considered as an ideal drug for designing a sustained release formulation.

- Floating tablets were developed to prolong the gastric residence time and increase drug bioavailability.
- Ritonavir was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract.
- FTIR studies concluded that there were no interaction between drug and polymer.
- Tablets were prepared by direct compression technique, using polymers such as HPMC K4M, K15M, K100M, and other standard excipients. According to this formulation codes F1, F2, F3, F4, F5, F6, F7, F8, F9, and F10 were prepared.
- Tablets were evaluated for physical properties, viz. hardness, friability, weight variation, *in-vitro* Buoyancy and Swelling studies etc. Further, tablets were evaluated for *in vitro* release characteristics for 12 hrs. Drug release kinetics

was studied for zero order, first order, Higuchi order and Korsmeyer-Peppas order.

6.1. CONCLUSION

From the above study it can be concluded that promising controlled release by gastro retentive floating tablets of Ritonavir was developed using different ratios of HPMC K4M, K15M and K100M

- The floating tablet of Ritonavir was capable of maintaining plasma drug concentration through 12 hrs.
- The formulation F7 was selected as an optimized formulation because it gave the best result in terms of the required *in-vitro* buoyancy study, good floating integrity and drug release in sustained release manner.
- The release profile of the optimized formula, fitted best to Zero order kinetics with R^2 value of 0.999.
- As the n value for the Korsmeyer-Peppas model was found to be less than 0.698, it follows Non fickian type of transport.
- Short-term stability studies indicated no appreciable changes in the drug content and *In-vitro* drug release rates of formulation F7.

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