Chapter 1
Introduction

INTRODUCTION

Though the monarchy of drug delivery system (DDS) has metamorphosed from conventional oral solid dosage form to complex DDS, oral route has overtly been the most sought by patients and pharmaceutical industry. Oral ingestion is the prime and most preferable route for drug delivery mostly due to their ease of administration, patient compliance and simplicity for scale up. [1, 2] Following oral administration majority of active pharmaceutical ingredients have to be absorbed into the blood to produce systemic action. However, certain drugs have "region-specific absorption" or "absorptive window", precipitates at different pH, poor stability in some gastrointestinal regions, drug-drug interactions and presystemic metabolism in the gut wall which ultimately leads to issues like low oral bioavailability [3, 4].

Enterosoluble formulations are intended to dissolve in intestinal fluid [5, 6]. Enterosoluble dispersion can be a beneficial approach in delivering molecules more successfully to desired site of action. It can improve drug delivery in common disease like Ulcers, Tuberculosis, Heart disease, etc. thereby benefitting to the people.

RATIONALE OF ENTEROSOLUBLE FORMULATIONS

1. To minimize drug-drug interaction of two drugs by segregated drug delivery; Rifampicin and Isoniazid
2. To protect the acid labile drug from acidic stomach environment and specifically targeting its release in intestine; model drug Lansoprazole
3. To improve solubility and prevent precipitation of weakly basic drug at intestinal pH; model drug Dipyridamole

PART A: SEGREGATED DRUG DELIVERY OF TWO INCOMPATIBLE DRUGS: RIFAMPICIN AND ISONIAZID

Tuberculosis – Delineating the Disease

Tuberculosis (TB) is one of the topmost infectious eradicators since decades all over the world. TB occurs in every part of the world and is considered as worldwide crisis from many years. Pragmatically, no country has ever eliminated this disease till now. TB is an infectious bacterial disease, caused by *Mycobacterium tuberculosis (M. tuberculosis),* which most commonly affects lungs. It can be transmitted from an infected individual to an uninfected individual via droplets or nuclei that are inhaled and lodge within the alveoli in the distal airways [7, 8]. Subsequently, *M. tuberculosis* is taken up by alveolar macrophages, thereby initiating a surge of events which ultimately ends in either triumphant containment of infection or progression to active disease. In healthy people, infection with *M. tuberculosis* often causes no symptoms, since the person's immune system acts to "wall off" the bacteria. The common symptoms of active TB of the lung in infected individuals are coughing with sputum or blood sometimes, weight loss, chest pains, weakness, fever and night sweats [9-11].

According to global TB report (2012) of World Health Organization (WHO), as of now the burden of TB is highest in Asia and Africa. India and China together solely account for almost 40% of the world's TB cases. About 60% of cases are in the south East Asia and western pacific regions. With respect to case notifications, 5.8 million newly diagnosed cases were notified to national TB control programmes conducted by WHO in 2011. The combat against TB since years have appear to be winning from the same report stating that new cases fell at a rate of 2.2% between 2010 and 2011. The report also mentioned that the TB mortality rate decreased 41% since 1990 and at the moment the world is on a track to achieve the global target of 50% reduction by 2015. While foreseeing most difficult Multi Drug Resistant-TB (MDR-TB) cases amongst worldwide, 3.7% of new cases and 20% of antecedently treated cases were projected. China, India, the Russian Federation and South Africa have captured almost 60% of the total cases of MDR-TB throughout the world [12].

Notably, childhood TB has always been remained as focal point with regard to establishing an accurate diagnosis and dose adjustment [12, 13]. The foremost common clinical manifestations of pediatric TB are pulmonary parenchymal disease

and intrathoracic adenopathy, accounting for 60% - 80% of child cases. Many a times, in children less than 12 years of age, the diagnostic smear appears to be false negative, thus underestimating as well as permitting the disease to cross above danger line and eventually making it uncontrollable. With respect to TB diagnosis in children, there is merely little prospect of achieving a gold standard from widely available means i.e. culture, microscopy, polymerase chain reactions based tests or serological testing. Hence, clinicians have to altogether rely on clinical criteria, chest radiography, tuberculin testing and concomitantly attempts must be made to enhance the prognostic power of available diagnostic tools [13].

Recently WHO has published a document regarding dosage regimen for the use of currently available fixed-dose combinations (FDCs) meant for children. Comparison of preceding and current WHO recommendations for dosage regimen in children on dose by weight basis is depicted in Table 1 [14, 15] and for FDCs is depicted in Table 2 [14, 15]. Global TB report also reported that estimating the burden of childhood TB (aged less than 15) was tough. According to the report, there were an estimated of 0.5 million cases and approximate 64000 deaths amongst children in 2011 [12].

Table 1: Comparison of previous and current WHO recommendations on dose by weight of first line Anti-TB drugs for children.

	Previous recommendation (mg/kg/day)	**Current recommendation (mg/kg/day)**
Rifampicin	8 to 12	10 to 20
Isoniazid	4 to 6	10 to 15
Pyrazinamide	20 to 30	30 to 40
Ethambutol	15 to 20	15 to 25

Table 2: Current FDCs strengths approved by the WHO-UN prequalification program for child treatment

Drug combination	**Strength**
Rifampicin + Isoniazid	RIF 60 mg + INH 30 mg dispersible
Rifampicin + Isoniazid + Pyrazinamide	RIF 60 mg +INH 30 mg + PZ 150 mg dispersible
Rifampicin + Isoniazid	RIF 150 mg +INH 75 mg tablet
Rifampicin + Isoniazid + Ethambutol	RIF 150 mg + INH 75 mg +EMB 275 mg tablet
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol	RIF 150 mg + INH 75 mg + PZ 400 mg + EMB 275 mg

One of the major hurdles in the conventional treatment of TB is that patients have to take an enormous quantity of tablets, usually 9-16 per day for 2 months (initial phase of treatment), followed by 3-9 tablets daily for 4-6 months (continuation phase). Current TB treatment usually recommends FDCs therapy to avert the emergence of multiple drug resistant organisms. Additionally using FDCs, the number of tablets to be taken can be reduced to as few as three or four per day for the entire course of the treatment. Effective treatment of TB patients with short course multidrug chemotherapy is the keystone of the modern approach to the control of the disease. Use of FDCs tablets against TB is moreover recommended by WHO and the International Union Against Tuberculosis and Lung Disease (IUTALD) as an additional step in ensuring proper treatment [16, 17]. The present day short course chemotherapy (SCC) regimens consist of four first-line anti TB drugs namely rifampicin (RIF), isoniazid (INH), pyrazinamide (PZ) and ethambutol hydrochloride (EMB) used in an initial intensive treatment phase of two months and further in continuation phase [16, 17]. The recommended daily doses and range of first-line anti-TB drugs are: INH 5 mg/kg/day (4 to 6 mg/kg/day), RIF 10 mg/kg/day (8 to 12 mg/kg/day), PZ 25 mg/kg/day (20 to 30 mg/kg/day), and EMB 15 mg/kg/day (15 to 20 mg/kg/day) [10, 12, 13] Table 3 depicts the FDCs strengths recommended by WHO [16, 18, 19].

Table 3: WHO recommended FDCs strengths.

Drug	Strengths (in mg)
Daily Use	
Rifampicin +Isoniazid+ Pyrazinamide+ Ethambutol	RIF 150 +INH 75 +PZ 400+EMB 275
Rifampicin+Isoniazid+Pyrazinamide	RIF 150+INH 75+PZ 400
Rifampicin +Isoniazid	RIF 300+ INH 150 RIF 150+ INH 75
Isoniazid + Ethambutol	INH 150+ EMB 400
Intermittent use (3 times Weekly)	
Rifampicin +Isoniazid+ Pyrazinamide	RIF 150 +INH 150 +PZ 500
Rifampicin +Isoniazid	RIF 150 +INH 150

Pathogenesis of TB

The tubercle bacillus was first identified by Robert Koch in 1882. The literature further also revealed *M. tuberculosis* as the origin of TB in humans [20]. *M.*

tuberculosis is a Gram-positive aerobic rod shaped acid-fast bacillus which is highly infectious, airborne and slow growing. Moreover, its cell wall comprises of high lipid content which facilitates the bacteria to survive within macrophages [8, 21, 22]. Though TB is caused by *M. tuberculosis*, environmental factors play a critical role in its causation [23]. When person with infected pulmonary TB cough, sneeze, speak, sing, or spit, they oust infectious droplets. The aerosolized bacteria containing droplet nuclei diameter of 1-5 μm spreads the infection to uninfected person via airborne dissemination of bacteria. Upon inhalation of the infected bacilli, they reach the alveoli, where they attack and replicate within the endosomes of alveolar macrophages [24, 25]. These bacterias are identified as the foreign substance by the macrophages and therefore they attempt to eradicate it by phagocytosis. During this process, entire bacteria is covered by the macrophage and stored temporarily in vesicle called phagosome which combines with lysozyme to create phagolysosome. In this phagolysosome, the cell attempt to kill the bacteria but however due to thick waxy mycolic acid capsule of *M. tuberculosis* protects it from toxic substances.

After the initial infection, intracellular replication of bacilli occurs and propagation of organisms may result through haematogenous routes and lymphatic routes. [26]. The hematogenous transmission can also spread infection to more distant sites, such as peripheral lymph nodes, the brain, kidneys, and the bones [24, 25, 27]. It should also be taken into consideration that about 90% of the infected individuals with *M. tuberculosis* have asymptomatic, latent TB infections, with only a 10% lifetime chance that the latent infection will progress to manifest, active tuberculous disease [28, 29].

TB is one of the granulomatous inflammatory diseases which leads to caseation in various tissues. The formation of granuloma is pathologic hallmark of primary and reactivation TB. Granulomas are formed by aggregation of macrophages, B lymphocyte, T lymphocytes and fibroblasts. The lymphocyte surrounds the infected macrophages. A giant multinucleated cell is formed in alveolar lumen when other macrophages attack the infected macrophage [30]. Resultant bacteria inside the macrophage can become dormant resulting in latent infection. Alternatively, liquefication of the caseous material may occur, with caseous necrosis and cavity formation resulting from sensitivity to *M. tuberculosis* proteins. The reason for the pathological tissue damage is supposed to be hydrolytic enzymes and oxygen radicals

which are produced by macrophages and neutrophils together by cytokines produced by mononuclear cells at the site of infection [9, 22-30].

Statement of Problem

Use of FDC have become now a days a routine practice and also recommended by WHO and IUATLD due to potential advantages like better patient compliance, reduced risk of emergence of multi-drug resistance TB, better dosage adjustments and management, simplify shipping and management, etc. [31]. Therefore, extensive efforts have been made worldwide to encourage use of FDC in TB therapy [32]. However due to quality problems in the FDC, several solemn concerns have been raised worldwide regarding its usage. Since decades FDCs finds two major drawbacks; fall in bioavailability of RIF when combined with other anti TB drugs and instability of the formulations resulting in variant pharmacokinetic profiles [33-35]. Acocella in 1989 first time highlighted the bioavailability problems related to FDC. They observed that one out of three FDCs containing RIF and INH, and all four FDCs containing RIF, INH and PZ had noteworthy inferior plasma concentrations of RIF [36, 37]. The stability related problems include changes in drug strength, alteration in dissolution profile, increase in degradation product levels, gain in moisture, etc. To address the bioavailability problems of FDCs, several efforts have been put by WHO and other international agencies which include development of the bioequivalence study protocol, addition of FDCs in the WHO Model List of Essential Drugs, identification of laboratories for carrying out bio-equivalence studies, development of a system intended for pre-qualification of products and training of the regulatory staff to evaluate applications for registration of FDC tablets [32, 34].

Moreover the variable bioavailability of RIF has been found to be a key hurdle in effective implementation of FDCs in TB programs [16, 38]. Moreover it is the chief drug that can be used in all the categories of the patient in both the phases (intensive and continous) of TB treatment. Furthermore, bacteriological and clinical investigations have also disclosed that the anti-mycobacterial activity of RIF is dose-dependent [39]. Thus, use of sub standard FDC or poor RIF bioavailability will ultimately result in treatment failure and also encourages development of multi-drug resistance TB strains [40].

Several factors have been proposed in the literature as reasons for poor oral bioavailability of RIF from different FDC formulations. They include raw material characteristics, particle size, changes in crystalline forms, manufacturing variables, process variables, changes in excipients, etc [16, 41]. However, effect of these factors has not been persuasively explained in previous studies [20].

In depth research have been conducted in the areas of problems related to FDCs and particular causes that explains the stability and bioavailability hiccups of FDCs have been proposed. *Explicitly, the mystery have been resolved by showing that the problem arises due to drug drug interaction between RIF and INH under empty stomach conditions which causes momentous loss of drug leading to poor oral bioavailability of RIF. Singh et. al. reported mechanism demonstrating that RIF is first hydrolyzed under acid conditions to 3-formylrifamycin, which reacts further with INH to form isonicotinylhydrazone (HYD). The HYD converts back to INH and 3-formylrifamycin, resulting in recovery of INH, but eventually inflicting the loss of RIF. The mechanism involves interaction of imine group of RIF with amino group of INH which yields HYD even in solid formulation environment* [34, 35, 42, 43] *Thus enhanced degradation of RIF in acidic medium in the presence of INH is one of the explanations for the poor bioavailability of the FDCs* [34, 35]. The same phenomenon of INH triggering the degradation of RIF in acidic medium was reported by Shishoo *et. al.* [44]. Thus, due to this drug drug interaction between RIF and INH in FDCs, less RIF is available for absorption as compared to RIF administered alone. This will be reflected in the poor bioavailability from the former formulation.

The studies carried out by researchers further demonstrated that this reaction between RIF and INH to form HYD has also been found in solid formulation environment as stated above and is augmented by humidity, light and temperature [35, 45]. Hence, this solid solid interaction is critical and serious matter in tropical countries where there is high temperature and humidity.

Moreover this reaction between RIF and INH is accelerated when PZ and EMB, the two co-drugs are present in FDCs. The grounds is the making of an acidic hydrolylic environment upon moisture uptake by EMB [34]. In depth, mechanism involves postulation that PZ and ETH exhibit a catalytic role through involvement of intra-molecular proton transfer during reaction between RIF with INH, which is conceived

to occur through a base-catalyzed transhydrazone formation process entailing a tetrahedral mechanism [46]. Thus the problem is even of more concern when in three or four drug FDCs than only combination of two drugs as stronger physical and chemical interaction exists in three or four drug FDC.

Rationale of developing the novel FDC of RIF and INH

The drug delivery systems (DDS), which contemplates the carrier, the route and the target, has evolved into processes designed to enhance the efficacy patient compliance, reduced side effects, etc. This may involve augmented bioavailability, improved therapeutic index, improved biopharmaceutical properties, enhanced patient compliance, reduced side effects, etc. [9, 47]. Amongst realm of DDS, oral route unambiguously, has been most sought especially in under developed or developing countries to epitomize the objectives like cost-effectiveness, feasibility and save resources [48]. Of various oral DDS, site specific prolonged release formulations endow to be of greater interest to formulation scientists for ensuring optimal bioavailability or improve biopharmaceutical properties [9]. Moreover, the development and evaluation of novel oral drug delivery system in form of a revitalized formulation can give a new lease of life to old but potential molecules especially for TB. Such type of drug delivery system can bring both therapeutic and commercial value to healthcare products.

RIF is the vital component in the current therapeutic treatment for TB having excellent effect even on dormant TB bacilli and is currently one of the frontline drugs recommended by WHO. Though it has excellent anti TB activity, it has many pitfalls like short half-life (1.5 to 4.5 h), pH-dependent degradation, adverse effects, bioavailability hiccups and concentration dependent autoinduction of its own metabolism which ends up in decrease in its bioavailability after repeated oral administrations [49]. Concerning its solubility it is reported that RIF is more soluble at low pH (pH 1.5, 1 in 5 of 0.1 M HCl, at 37 ◦C), while it is less soluble at higher pH (pH 7.4, 1 in 100 of phosphate buffer, at 37 ◦C) [50]. Prankerd *et. al.* reported solubility of RIF at 25 ◦C is 1 in ∼10, 250, and 360 parts of water at pH 2, 5.3, and 7.5, respectively [51]. Concerning its permeability, permeability studies have revealed that RIF is well absorbed from stomach owing to its better solubility which was

maximum between pH 1-2 [52]. It is also stated that site specific sustained drug delivery in stomach of RIF could be beneficial in improving its bioavailability [9, 53]. One of the major drawbacks in the use of INH for the treatment of TB is the severe toxic/adverse effects associated with it; primarily hepatotoxicity because of metabolism of INH, especially acetylation, by N-acetyltransferase [22, 54, 55]. The effect is genetically prominent in rapid acetylators leading to plasma concentrations approximately one third to half of that in slow acetylators and average half-lives are less than 1 hour to 3 hours, respectively. Moreover these toxic effects lead to discontinuation of the therapy because of the lack of patient compliance which results in subtherapeutic concentrations of the drug in the blood, leading to treatment failure and also encourages the INH resistant strains of *M. tuberculosis* [56, 57]. Secondly, as addressed in earlier studies that in the acidic pH of stomach, RIF reacts with INH to form an insoluble compound 3-formylrifamycin resulting in reduction of bioavailability of RIF to the extent of 30% [53, 58]. Moreover, permeability studies have demonstrated INH is less permeated through the stomach due to its protonated form at acidic pH (pKa=2) and is well absorbed through all the three segments of intestine [52].

This aspect prompted the development of enteric coated sustained release (SR) formulations of INH to optimize the blood levels especially in the rapid acetylators, reduce side effects, minimize interaction with RIF by minimal release in gastric environment and ultimately improve patient compliance on long term tuberculosis therapy.

The objective of the work was to prepare two enteric coated sustained release formulations viz., tablet and pellet dosage forms for INH.

The objective of the work was also to prepare floating SR dosage form of RIF which gradually release it in acidic medium to minimize the concentration-dependent degradation of RIF and simultaneously provide sustained release action. This formulation was an add on formulation prepared to study interaction and degradation of RIF in presence of developed INH formulation from its FDC. Hence, the purpose was to formulate both RIF and INH in single formulation and investigate the degradation of RIF in presence of enterosoluble INH formulations. The final formulation will be single capsule containing RIF tablet and INH tablet/pellets.

In nutshell, the research work proposed encompasses formulations retaining RIF in stomach and delivering INH in intestine thereby segregating there release and minimize its above said pitfalls.

Formulation Design

Fig. 1 portrays the holistic approach for development of FDCs of INH and RIF.

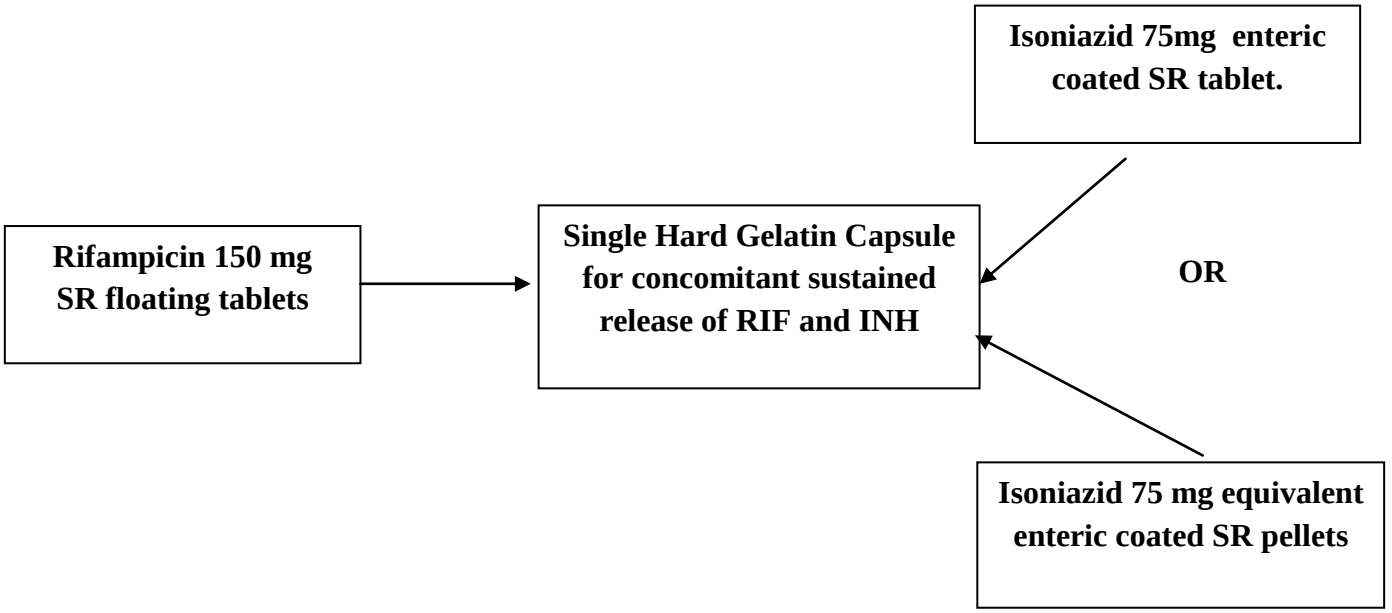

Fig.1: The holistic approach for development of FDCs of INH and RIF.

The two proposed formulation of INH will release in sustain manner at intestinal pH without releasing in stomach. Mean while RIF will retain in sustain manner in stomach by preparing its floating dosage form. Thus, RIF will be restrained in stomach while INH will be released in intestine. Thereby drug drug interaction will be minimized by physical segregation of two drugs and interaction will be minimized.

Extended drug delivery system

As discussed oral ingestion is the prime and most preferable route for drug delivery mostly due to their ease of administration, patient compliance and simplicity for scale up [1, 2]. Moreover, recently significant consideration has been stressed on the development of controlled drug delivery system due to its several benefits [1, 2, 9]. Sustained release dosage forms comprises of dosage forms that endow with medication over an extended period of time. Recent years have witnessed spurts in development more and more sophisticated sustained and controlled drug delivery systems. On administration of immediate release oral tablet formulation provides

quick rise in plasma drug concentration which than declines. On the while, if elimination is fast, therapeutic action will last only for shorter period of time during which plasma drug concentration is within shorter period of time. Thus a dosage form which provides optimal control of plasma concentration within therapeutic window for prolonged period of time would be beneficial in averting many pitfalls [59, 60].

Fabrication of a successful sustained release dosage form is usually not easy and involves contemplation of many factors like physicochemical properties of drug, route of administration, pharmacokinetic nature of drug, disease condition to be treated, drug incorporation behavior in dosage forms, etc. [60].

Preferably sustained release formulations are designed in a way to release rapidly some pre-determined fraction of total dose which is generally referred as loading dose. The loading dose will elicit the desired pharmacological response as early as possible. The remaining fraction of the total dose which is generally referred as maintenance dose is then release at constant rate for the extended period of time as per formulation designed [61, 62].

Classification of sustained/controlled release systems [62-66]

(A) Diffusion Controlled System

(a) Reservoir Devices

(b) Matrix Devices

(B) Dissolution Controlled Systems

(a) Encapsulation Dissolution control

(b) Matrix Dissolution Control

C) Diffusion and Dissolution Controlled (Bioerodible)

Advantages of sustained release dosage forms [62-66]

- Reduced dosing frequency
- . Reduced fluctuation in therapeutic drug concentration in blood.
- Avoidances of night time dosing
- Enhanced patient compliance
- More uniform effect
- Reduced side effects
- Effectual utilization of drug

Disadvantages of sustained release dosage forms [62-66]

- High cost

- Unpredictable or poor in vivo in vitro correlation
- . Dose dumping
- Reduced potential for dosage adjustments
- Administration of sustained release formulations does not allow the prompt termination of therapy.

Introduction to matrix systems

Monolithic (matrix) devices are probably the most common of the devices for controlling the release of drugs. This is mainly because of its traits like ease to fabricate as compared to reservoir systems and they are less perilous of causing dose dumping that could result from rupture of the membrane from reservoir device. In matrix system, the drug is dispersed within the polymeric matrix and is typically manufactured by the compression of a polymer/drug mixture or by melting. The drug release from the monolithic matrix devices may depend upon the solubility of the drug in the polymer matrix or if the case is of porous matrixes, it depends upon the solubility in the sink solution within the particle's pore network and also on the tortousity of the network dependent on whether the drug is dissolved or dispersed in the polymer [62-67].

Matrix tablets are believed to be the commercially feasible for sustained release formulations as it involves the minimum processing variables, employ the conventional amenities and can incorporate large doses of drug. One approach to manufacture sustain release tablet is direct compression in which blend containing drug, retardant materials and other excipients are homogenously mixed and directly compressed to form tablet. Alternatively, blends can granulated first and then compressed to form tablet. There are basically three classes of retardant materials used to prepare sustain release matrix tablet. The first class comprises of retardant material that form insoluble "Skeleton" matrices. The second class consists of water insoluble materials that may be erodible in nature and the third class consists of polymers that form hydrophilic matrices [68].

The tablets prepared from the insoluble materials are intended to be ingested intact and not to break apart in the gastrointestinal tract. The examples of hydrophilic polymers used as release retardant polymers are hydroxypropylmethyl cellulose, polyethylene oxides, sodium carboxymethyl cellulose, etc. while that of hydrophobic

polymers include ethyl cellulose. In case of tablets prepared from hydrophilic polymers, they swell when comes in contact with biological fluids and form a strong viscous barrier that controls the drug release [62-68].

In the research undertaken, INH will be prepared as sustained release core tablet to give extended release in pH 6.8 phosphate buffer. The sustained release matrix tablet will be prepared from preferably combination of hydrophilic and hydrophobic polymers. The monolithic matrix tablet will release initially faster as loading dose and thereafter will provide sustain action in pH 6.8 phosphate buffer. The optimized sustained release matrix core tablet will be enteric coated to resist drug release in 0.1 N hydrochloric acid. After following acid stage dissolution the core tablet will provide sustain release action in pH 6.8 buffer.

Gastroretentive drug delivery system

Though susutained drug delivery offers many advantages, for certain drugs, extending the gastric retention is desirable for achieving greater therapeutic benefit. The gastroretentive DDS can improve the controlled delivery of the drugs by continuously releasing the drug for a prolonged period at the absorption site i.e. stomach; thus ensuring its optimal bioavailability [69].

This type of formulations that provide extended residence times in the stomach are highly desirable for drugs that are locally active in the stomach, drugs which have an absorption window in the stomach, drugs that are unstable in intestine/colon, drugs that exhibits lower solubility at higher pH, etc. Moreover, by prolonging the gastric residence time these systems can be efficaciously employed as sustained release formulations as discussed above, thereby reducing the dosing frequency and enhancing patient compliance. Various approaches that can be employed to increase the gastric residence time of oral dosage forms include:

- Floating systems
- Bioadhesive devices
- Low density systems
- Swelling and expanding systems
- Modified shape systems
- High density systems
- Super porous hydrogel systems [70-73].

Floating drug delivery systems is one of the imperative approaches to achieve gastric retention and thereby ensuring drug release for prolonged period at absorption site. These type of systems have bulk density lower than the gastric fluid and therefore they remain buoyant in the stomach for extended period of time without majorly been affected by gastric emptying rate thereby releasing the drug slowly at desired rate from the system. When the drug is completely released or after the release of the drug, the residual system remaining is emptied from the stomach. Thus this type of system have almost all the advantages of sustained drug delivery system like reduce dosing frequency, reduce fluctuations in plasma drug concentrations, reduce side effects, etc. [70-75].

Various approaches for floating drug delivery system include hydrodynamically balanced systems, . Gas-generating systems, . Raft-forming systems, . Low-density system, etc. [70-75]. Of these various approaches effervescent or gas generating system approach have been selected for designing and formulating floating drug delivery system. This type of effervescent matrix system can be prepared with the help of polymers and various effervescent compounds like sodium bicarbonate, citirc acid, and tartaric acid. When this type of dosage forms comes in contact with the acidic gastric fluid, carbon dioxide is liberated and gets entrapped in the dosage forms which will ultimately provide buoyancy to the system and make them float in the stomach [70, 71, 73, 74].

Here, as discuused above RIF will be formulated as floating tablet employing effervescent agent for its stomach specific delivery to improve its biopharmaceutical properties, decrease concentration dependent autoinduction of its own metabolism, prevent its interaction with INH and able to get absorbed from its preferable site of action.

Multiparticulate drug delivery systems

The dosage forms that are administered orally can be generally classified into two groups: single unit and multiple unit dosage forms. The single unit devices comprises of tablet or capsule while multiple unit comprises of pellets or microencapsulated drug either filled into capsule or compressed into tablet. Pellets are contemplated to be of enormous interest in academic research and pharmaceutical industries due to its reasons like flexibility in designing dosage form and can improvise efficiency and

safety of bioactive agents. Pellets are agglomerates of fine powder particles exhibiting nearly spherical or cylindrical in shape and narrow particle size distribution. They are generally in the size ranges of 0.5 to 1.5 mm and its size depends on the manufacturing technology employed [76, 77].

The advantages of the pellets include the following [76-78].

- Pellets generally demonstrate good flowability due to generally uniform size and spherical shape which reduces capsule filling problems.
- They have high physical and chemical integrity which provides minimal friction during flowability and produces minimal dust generation.
- Facilitates coating due to spherical shape and low surface area to volume ratio.
- Maximize drug absorption due to freely dispersion in gastrointestinal tract.
- Reduce variations due to gastric emptying rates.
- Reduces intra and inter subject variability.
- Less chances of dose dumping when formulated as modified release dosage forms.
- Allows formulating two or more incompatible drugs into single formulation.

Pelletizing techniques

Several manufacturing techniques are there for manufacturing of pellets. They can be broadly grouped in diverse ways depending upon production technique employed, equipment type, strength of mechanical forces involved, etc. The following are the general techniques used to manufacture pellets [76, 78, 79]:

- Extrusion and spheronization
- Solution/suspension layering
- Powder layering
- Direct pelletization

Extrusion - spheronization

Extrusion and spheronization is one of the approaches used to manufacture and prepare pellets. They offer advantages like ease of operation, high throughput with low wastage, manufacturing of pellets with low friability and suitable for film coating, functional coating, etc. [80, 81].

The various steps involved in preparing pellets by extrusion spheronization involve initially dry mixing of the drug with excipients than granulation to obtain a wet mass. The wet mass is extruded using extruder and the extruded material is subsequently transfer to spheronizer where the extrudes are broken to produce spherical shape using rotating friction plate. Finally the pellets are dried into dryer and after drying screened to obtain require particle size. During extrusion shaping of the wet mass occurs by passing it through the extrusion die to obtain long rods i.e. extrudates of wet mass [82]. During spheronization the extrudates undergo number of shape changes to finally obtain spheroids using friction plate under controlled conditions [82, 83].

Extrusion-spheronization to produce matrix pellets for sustained release

Generally sustained release in the pellet system is usually obtained through polymeric coatings. But recent years have witnessed spurts in development of sustain release matrix pellets due to drawbacks of polymeric coatings like [84]

- Time consuming process and expensive.
- Variability in film thickness.
- Difficulty in reproducing drug release profiles due to inconsistent film coating.
- Many time cracks are observed in film coating.
- Coating is dependent on optimization of several parameters.

The matrix system comprises of the heterogenous distribution of drug particles into polymeric matrix where the drug is release by diffusion through the matrix, erosion of the matrix or combination of both [60, 85, 86].

Fluid bed coating of pellets

The fluid bed coating works on the principle on fluidizing the particles and spraying the coating fluid onto it which are subsequently dried. In fluid bed coater coating and drying takes place in one single machine. Polymeric solutions or dispersions with other excipients as dissolved or suspended are applied onto the core for film coating. Upon drying of the solvent, the polymer and other additives remain onto the core as uniform film. Film formation from solutions or dispersion occurs by different mechanism [87]. Alternatively, functional polymers can also be applied to coat the pellets for functional properties. Several polymers like Methacrylic acid copolymers,

shellac, hydroxypropylmethyl cellulose acetate succinate, etc. can be employed for enteric coating of dosage forms [88].

Fluid bed coatings are of three types [89, 90]:

1. Top spray coating

In top spray coating, the particles are fluidized in the flow of the heated air that is introduced via base plate into the product container. The coating liquid is sprayed counter currently against the direction of air or airflow by means of a nozzle. Drying takes place by continuous moving of the particles upwards in the direction of airflow.

2. Bottom spray coating (Wurster coating)

Wurster process offers an advantage of complete sealing of the surface with low usage of coating substance. In wurster process, nozzle is fitted in the base plate and spray pattern is concurrent with the feed. Wurster coating uses a Wurster cylinder and a base plate the particles are accelerated inside the Wurster tube and interact with the spray cone concurrently. When the particles travel upwards they get dry and fall outside the Wurster tube towards the base plate. Than the particles are guided to the in die of the tube from outside where they are again accelerated by spray. The Wurster coating produces particularly more even film and different particle sizes are also evenly coated.

3. Tangential spray coating (Rotor pellet coating)

The tangential coating is particularly beneficial for coating with high solid content. The particles are set into the spiral motion by means of rotating base plate. Here the nozzle is arranged tangentially to the rotor disc with concurrent spray pattern into the bed. Moreover, very thick film layers can also be applied by rotor method. Bottom spray is usually preferred for coating purpose while top and tangential spray for granulation purpose.

INH sustained release matrix pellets will be prepared by extrusion and spheronization which will be subsequently enteric coated using wurster process in fluid bed coater for restricting its release in 0.1N HCL. After 2 hr of dissolution in 0.1N HCl, the pellets will provide sustained drug delivery at pH 6.8 phosphate buffer. Both the loading dose and maintenance dose will be provided by sustained release pellets.

PART B: TO PROTECT THE ACID LABILE DRUG FROM ACIDIC STOMACH ENVIRONMENT AND SPECIFICALLY TARGETING IT'S RELEASE IN INTESTINE: LANSOPRAZOLE

Several upper gastrointestinal disorders like peptic ulcer, gastroesophageal reflux disease (GRD) and Zollinger-Ellison Syndrome (ZE) share common anomalies like too much acid and pepsin activity. Peptic ulcer is typically characterized by existence of ulcers in any region of GIT exposed to acid in adequate concentration and duration. The ulcers are not only occur in the stomach i.e. gastric ulcer or small intestine i.e. duodenal ulcer but also occur in esophagus i.e. Barrett's esophagus [92]. Peptic ulcers are characterized by lesion in a membrane which is developed in regions of GIT due to exposure to acidic gastric juice. The word 'peptic' is derived from the greek word 'peptikos' which means related to digestion [93]. In peptic ulcer disparity is observed between the aggressive factors like pepsin, acid, Helicobacter pylori (H.Pylori) and defensive factors like bicarbonate ions, gastric mucus and prostaglandins. Many a times innate resistance of mucosal cells is also observed along with above discussed factors [92]. There are several defense mechanism exhibited by normal gastric mucosa against aggressive factors [91].

The symptoms exhibited by uncomplicated peptic ulcer include epigastric pain which can be escorted by bloating, fullness, early satiety and nausea. Epigastric pain in the duodenal ulcer patients occur usually during the fasting state or during night. This epigastric pain is usually relieved by acid neutralizing agents or food intake [94].

Predisposing factors for peptic ulceration [91]:

- H. pylori infection.
- Non-steroidal anti-inflammatory drugs.
- Cigarette smoking.
- Diet.
- Psychological stress.
- Alcohol.
- Other diseases like short bowel syndrome, Crohn's disease, chronic pancreatitis, etc.
- Genetic factors.

Proton pump inhibitors

Proton pump inhibitors (PPIs) have been widely employed for treatment of various gastroesophageal diseases. The examples of clinically widely used PPIs are pantoprazole, rabeprazole, lansoprazole (LSP), omeprazole and esomeprazole [95].
Three major neuro-hormonal pathways regulate the parietal cell acid secretion. Acetylcholine regulates the neuronal secretion pathway and histamine and gastrin regulates the hormonal secretion. All the pathways meet on proton pump of parietal cells i.e. H+- K+ ATPase which is ultimately responsible for gastric acid secretion. HCL is secreted by the parietal cells at concentration of pH 0.8. It also keeps a median daily pH of stomach around 1.4 [96]. PPIs selectively inhibit H+- K+ ATPase of the parietal cells and thereby inhibiting the acid secretion. The terminal phase in gastric acid secretion involves the proton pump which is being liable for secretion of H+ ions into the gastric lumen. Thus inhibiting the gastric proton pump would be an ideal target for inhibiting secretion of gastric acid. All PPIs bind to the alpha subunit of the proton pump and thereby causes irreversible inhibition of H+- K+ ATPase. PPIs inhibit both basal and stimulated secretion of gastric acid, independent of the type of parietal cell stimulation [95-97].

Regarding their mechanism, PPIs gets converted into active sulfenamide metabolite by the acidic environment of parietal cells which further reacts with cysteines of enzyme H+/K+ ATPase. In depth, the protonation of PPIs forms irreversible disulphide bonds with the cysteine residues. Amongst them, the two most important are CYS813 and CYS822. This causes inactivation of sulphydryl group of the proton pump thereby reducing the hydrogen ion concentration. This conversion of LSP into active form should occur inside the gastric cells, thus it should be absorbed in intact form from the intestinal tract [98-100]. Thus PPIs as such are present in an inactive form. When they cross the cell membrane and reach into the intracellular compartments like parietal cell canaliculus where acidic environment prevails gets protonated and rearranges into active forms [95, 101-103]. This active will inhibit he proton pump as described above.

Statement of problem

It is well recognized that the LSP and other PPIs are susceptible to degradation in acidic media. Rate of degradation decreases with simultaneously increase in pH [104,

105]. Regarding its pharmacokinetics, absolute bioavailability > 80%, plasma half-life 1.5 hours, time to peak plasma level 1.7 hours and protein binding about 97% [98, 99]. However, wide intersubject variation has been observed in its bioavailability which may be attributed due to genotype variation of CYP2C19, possible degradation by the gastric acid and limited solubility in water [106].

Therefore there is a need to develop a system which protects LSP from acidic pH and also addresses its solubility issues.

Rationale for developing spray dried enteric microparticles of LSP

Thus research undertaken focuses on preparation of enterosoluble microparticles by spray drying procedure for its enteric delivery and also improving its solubility. The developed microparticles will have all the advantages of multiparticulates systems like uniform distribution in gastrointestinal tract, less affected gastric emptying rate and gastric transit time, less susceptible to dose dumping, attain more constant plasma levels, etc. [107, 108]. Moreover, it would also have benefits like production via continuous one step process and prudent prospects of scale up. As enteric polymers contain acidic functional group; it may degrade acid labile drug like LSP. The proposed work encompasses priorly dispersing of enteric polymers at higher pH to make it soluble [109].

Formulation Design

Since many years encapsulation of drugs into polymeric particles have been widely employed. Microencapsulation refers to incorporation of therapeutic active drugs into particles like polymers or phospholipids [110]. They have been widely employed in pharmaceutical industries for purposes like control release, protection from pH or hydrolytic resistance, masking of taste or odors, enhance stability, reduce toxicity, to alter pharmacokinetics, etc. [111, 112]. Microparticles have generally particle size in the range of 1-1000 μm. They are further classified into two types which are microspheres and microcapsules. When the microparticles are fabricated as matrix system, it is termed as microspheres and when they are fabricated as reservoir systems, they are termed as microcapsules [113].

Following are the various techniques used to prepare microparticles [113, 114]:

- Solvent evaporation and extraction based processes.
- Phase separation coacervation
- Spray drying
- Ionic gelation
- Chemical and thermal cross-linking

Amongst the various above techniques; spray drying seems to be highly fascinating due to its characteristics like fast particle formation and prudent prospects of scale up [115].

Spray drying technology for preparation of microparticles

Spray drying is a process which involves transformation of different liquid feed like suspension, emulsion into dry particulate form by spraying the product into hot drying medium. It is a continuous process and has been widely adopted and practiced in variegated industries like food, cosmetic and pharmaceuticals. Moreover it is suitable for both aqueous and organic soluble therapeutic substances. The basic process of spray drying is divided into three steps; atomization, drying and powder collection [113, 116-119].

The liquid feed is pumped and dispersed through an atomizer to generate fine droplets or mist of the liquid feed. The generated fine droplets are atomized in hot air or inert gas in the drying chamber. This causes bridging of the fine droplets and sufficient volume of warm air which will result subsequently into evaporation and drying of the liquid droplets. The heat of evaporation is supplied by the hot air and moreover due to large surface area, solvent removal step is also quick. The following dry product than interacts and pass through the cyclone which separates the product upon principle of centrifugal force and conveys the dried product to the collector. Finally, the air is exhausted with the moisture [113, 116-119].

Advantages of spray drying [113]

- It can be designed according to capacity required.
- Rapid and continuous process.
- Adaptation to fully automated system is possible for simultaneous control of various variables.

- Few movable parts.
- It can be used for thermolabile or heat sensitive material.

Disadvantages of spray drying [113, 120]

- Bulky equipment.
- Overall thermal efficiency is low.
- Yield related problems especially at laboratory levels.

Spray drying has widely employed to encapsulate variegated type of active ingredients [113, 120, 121]. Additionally as discussed above its advantages like scalability, fast process and can be operated for both batch and continuous process makes it fascinating approach for preparation of microparticles [110,113,122]. *Thus, here spray drying technology was selected to prepare enteric microparticles of LSP in single step. Additionally, preparation of microparticles in single step is advantageous over commercial available enteric coated dosage forms like tablets and pellets in capsules which involve multiple steps. Moreover, LSP may also be present in amorphous form in microparticles which will address is solubility issue.*

PART C: PREVENT PRECIPITATION OF WEAKLY BASIC DRUG AT INTESTINAL pH: DIPYRIDAMOLE

Poor oral bioavailability has remained unambiguously, a significant matter during drug development. Though numerous of them fail due to toxicity or lack of *in vivo* efficacy; numerous hurdles due to poor solubility, dissolution rate, unfavorable pharmacokinetic profile, etc. cannot be deny. Specifically, the rate at which a drug solubilizes and goes into solution is a vital determinant of drug absorption from the gastrointestinal tract. The variegated factors governing the absorption are drug's pKa, partition coefficient, crystalline and amorphous forms, pH of maximum solubility, lipid content of its environment, etc. [123-125].

Poorly soluble drugs many frequently demonstrate reduced and variable bioavailability upon oral ingestion. This solubility issue is predominantly complex in the case of ionizable drugs as most of the drugs are weakly acids, basic drugs or combinations of these two types. Therefore these type of compounds show pH dependant solubility which ultimately affects its bioavailability leading to inconsistent and variable clinical efficacy. Now in case of weakly basic drugs; they have lower pKa and remain in ionized form in the acidic pH of stomach. Thus at the stomach pH due to ionization of the basic drug they exhibit higher solubility resulting in adequate solubilization of drug. However, following transition to intestine environment, deprotonation of the free base can occur converting it unionized form which leads to lower solubility at intestinal pH. Depending upon the oral dose injested decrease in drug solubility can lead to supersaturation of drug with risk of precipitation. Now according to pH partition theory, weakly basic drugs can be better absorbed from the intestine due to of its unionized form at intestinal environment. Thus pH gradient effect influences the solubility of the weakly basic drug which may precipitate upon entry into intestine and influence systemic bioavailability of the drug molecules [123, 126-129].

Statement of problem

Dipyridamole (DPL) is a weakly basic drug having pKa of 6.4 and precipitates upon reaching small intestine. It is a BCS class II compound having poorly solubility in water and at elevated pH whereas it is soluble at acidic pH [123, 130]. Studies assessing the bioavailability of DPL have demonstrated that absorption is variable and

pH-dependent in humans [123, 131]. Additionally, its absolute bioavailability is reported in between 18- 43% [132]. Hence, formulations extending supersaturation following acid to neutral pH transition must be focused to address the above issue. Thus it can also be concluded that formulations maintaining supersaturation targeted to intestine might address the problem as satisfactory absorption is not attained when supersaturation is limited to gastric environment.

Rationale for developing solid dispersion with polymer and complex formation with pH modifier

To overcome above said pitfall, many formulation efforts have been carried out to improve drug absorption. Amongst them, making amorphous form is one of the approaches to improve solubility of the drug. When amorphous form of the drug dissolves, initial high supersaturation is created and only if this supersaturation is maintained precipitation will be inhibited and absorption will be improved. This task of production and maintenance can be fulfilled by employing various precipitation inhibitors that obstruct the drug nucleation and crystal growth. Polymers can be employed as precipitation inhibitors and solid state stabilizers for preventing precipitation from supersaturation [133]. Solid dispersion is one of the techniques where use of precipitation inhibitors can be efficiently employed to achieve the above goal [134, 135]. The objective of this work was to prepare solid dispersion of DPL and investigate its precipitation behavior. *Thus the aim was to prepare and evaluate formulations with polymeric carriers which lead to extensive supersaturation in acidic media and inhibit DPL precipitation in intestine by maintaining supersaturation upon the acidic to neutral pH transition.*

Another approach to improve solubility of weakly basic drug is to use acidifiers which keep the microenvironmental pH acidic, thereby increasing solubility of the drug [126, 136, 137]. *Hence, complex was prepared with fumaric acid and investigated for its effects on precipitation and solubilization of drug.*

Formulation Design

Solid dispersion unambiguously, is one of the promising technique for improving solubility and dissolution [138]. Solid dispersion involves dispersion of one or more active pharmaceutical ingredients into an inert carrier or matrix in solid state. The active substance in solid dispersions can be dispersed as amorphous particles,

crystalline particles or separate molecules while the carrier can be in the amorphous or crystalline state [139, 140].

The following are the mechanisms by which solid dispersions work [138, 140]:

- High-energy metastable state or amorphous form.
- Particle size reduction to nearly molecular level.
- Carrier molecules prevent or hinder aggregation of drug particles.
- Crystal growth is also inhibited by carrier.
- Intermolecular hydrogen bonding between drug molecule and carrier.
- Wettability is also improved.
- Porosity enhancement.

The following are the variegated methods for preparation of solid dispersions [138, 140, 141].

- Spray drying.
- Solvent evaporation.
- Fusion.
- Freeze drying.
- Spray-freeze drying.
- Solvent-fusion method.
- Hot melt extrusion.
- Quench cooling method.

Microenvironmental pH modification can be one of the most efficient approaches to improve the solubility of the drugs showing pH dependant solubility. The modulation of microenvironmental pH can be attained by addition of pH modifier in formulation which will lead to pH independent solubility. The pH modifier alters the microenvironmental pH in the diffusion area so as to generate a better environment for solubilization of drug. While the solubility of ionizable drugs could differ based on pH, minor differences in the microenvironmental pH around the drug would affect the level of enhancement in dissolution. Thus, changing the level of pH and maintenance of its duration could be the prime factors for enhancement of dissolution. The key criteria for selection of pH modifiers depend on pH solubility profile of drug, pH modifier's pKa and its aqueous solubility. The ideal pH modifier would be the one which not only modulates microenvironmental pH for high drug solubility but also maintain the condition for prolonged period of time [126, 142-144].

Thus the objective of the work was to prepare solid dispersion with polymers having diverse physical and chemical properties and investigate its effect on DPL precipitation behavior upon acid to neutral pH transition. Also effect of increase in molecular weight of respective polymers on stabilization of DPL supersaturation and precipitation were investigated. Finally, the other objective was also to prepare complex formation with pH modifier to improve dissolution in neutral pH conditions.

Overview of the dissertation

Chapter 1 of the research work contains introduction and the rationale for the work encompassed. It is bifurcated in three parts as per the rationale selected. Part A provides a glimpse on current TB scenario, its pathogenesis and hiccups with FDCs; especially of RIF and INH. The chapter also describes the considerations pertinent to the development of enteric coated SR formulations of INH and floating SR formulation of RIF. Important concepts of site specific prolong delivery simultaneously with segregated drug delivery to resolve hiccups of FDCs of RIF and INH are put forth. Part B describes the basic of PPIs and their mechanism of action. It also discuss the drawbacks of LSP and steps taken to pertinent to development of spray dried microparticles are presented. Part C discuss the important aspects of pH dependant solubility, precipitation at higher pH, and problems associated with bioavailability of weakly basic drug. The development considerations with approaches of solid dispersion and complex with pH modifier are also conferred.

Chapter 2 highlights the objectives and the specific aims of the each of the three parts of research work undertaken.

Chapter 3 describes the overall review of related literature for each of the three parts of research work undertaken.

Chapter 4 depicts list of the materials, solvents/reagents and equipments with respective to their supplier/manufacturer name.

Chapter 5.1 describes the overall Quality by Design (QbD) approach for stepwise systematic formulation development of site specific sustained drug delivery of INH tablets. Preliminary trials undertaken for selection of type of process for tablet preparation together with selection of polymers and binders are discussed. A 2^3 full factorial design having been employed for establishing design space of factors of core

tablet which fall under high risk category of Failure mode and Effects Analysis (FMEA). Lastly, process capability analysis employed on reproducibility batches for investigating spread of process have been discussed.

Chapter 5.2 portrays the QbD approach for formulation development of site specific sustained drug delivery of INH pellets. Preliminary trials were undertaken to investigate type and level of polymer giving not only sustained release but also viewing its feasible for extrusion process. Further development for obtaining sustained release profile and impact of type of binders and combination of polymers to achieve the same is also discussed. Finally, level of enteric polymer was also varied and optimized to get desired drug release profile similar to that core pellets after enteric coating ruptures.

Chapter 5.3 discloses the overall QbD approach for stepwise systematic formulation development of stomach specific delivery of RIF. Preliminary trials were undertaken for evaluation of type of wax and level of gas generating agent. Further various type of pore formers were investigated to understand its role in obtaining not only burst release but also providing sustain release after burst release. A Box-Behnken experimental design was employed for identification of the optimum system for various factors which needed through investigation according to FMEA analysis. Lastly, design space was established and process capability analysis performed on reproducibility batches is also discussed.

Chapter 5.4 elaborates the drug - drug interaction study from the developed novel FDC formulation of RIF and INH. The crux of the research work also describes the reduced formation of 3-Formyl rifamycin from the FDCs of INH SR tablet and RIF floating tablet and also from the FDC of INH SR pellets and RIF floating tablet. The 3-Formyl rifamycin formation from alone plain RIF and RIF floating tablet have also been discussed.

Chapter 6 describes in depth analysis of various enteric polymers on entrapment efficiency and gastric resistance of LSP spray dried microparticles. The various formulation changes made are also discussed. Finally, stepwise various process parameter were varied and optimized to study their impact on microparticle properties. Various characterization techniques like Differential scanning calorimetry, Powder X-ray diffraction, Fourier transform infra-red spectroscopy and Scanning

electron microscopy, etc. were undertaken to characterize nature of drug in microparticles, presence of drug – polymer interaction or not and morphology of microparticles respectively.

Chapter 7 describes through investigation and analysis of diverse type of polymers for preparation of solid dispersion and its effect on supersaturation and precipitation of DPL upon pH transition from their respective solid dispersions. Additionally, effect of molecular weight of homologous series of same polymer on supersaturation and precipitation upon pH transition have also been discussed. Secondly, effect complex prepared with pH modifier as an alternative approach to prevent precipitation of weakly basic drug DPL upon pH transition have also been described. Lastly, *in vitro* Caco-2 cell line studies were conducted to study effect of various formulations on enhancing permeability of DPL from it.

Chapter 8 concludes the dissertation work and ties together the significant issues addressed by formulation development for each of the three core parts of research work.

Chapter 9 enlists the publications arose from the research work encompassed. It also list the manuscript submitted for peer review and conferences/workshops attended during the tenure.

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