8.1 Summary of Research Findings

This thesis describes an investigation regarding novel concepts in systematic development of rapid dispersible tablets. Recently Rapid Dispersible Tablets introduced in Indian and international markets as a novel solid oral dosage form that improves patient compliance along with providing pharmaceutical advantages for the active drug. This research work investigated the formulation factors that control the preparation process and performance of rapid dispersible tablets based on the common excipients. Accordingly, the research was performed to explore and optimize novel concept of formulation technologies in development of dispersible tablets. As a result of this research, two novel systems that can address the rapid dispersion and release profile with effective taste masking such as co-micronization and an effective combination of dual technology (Solid dispersion and polymer coating) were studied.

8.1.1 Formulation of Rapid Dispersible Tablets with Novel Concept of Co-micronization

Successful development of rapid dispersible tablets of Tolfenamic Acid by implementation of co-micronization with diluents requires careful optimization of formulation parameters in order to obtain an optimal balance between various physical properties such as disintegration and dispersion time and analytical properties such as release profile of tablets.

On the basis of various physical and analytical evaluation of formulation the rapid dispersion and wetting of formulation can be easily achieved by simple incorporation of micronization of active with diluents. The co-micronization showed a promising effect in
the particle size reduction of Tolfenamic Acid and providing more surface area in enhancement of wetting and dispersion properties of formulations. The release profile of tablets was directly affected by changing the particle size of co-micronized blend in formulation. The release profile of blend without co-micronization retards the release profile of Tolfenamic Acid. The comparative evaluation of formulation F-1 (as reference formulation without micronization of active) proved the concepts of co-micronization in the Tolfenamic Acid Rapid Dispersible Tablets.

There were no significant changes observed on physical and analytical parameters of optimized formulation during study. So an effective and stable formulation of Tolfenamic Acid in dispersible dosage form can be developed by implementation of novel concept of co-micronization technology.

8.1.2 Optimization of Disintegrants and Particle Size in Rapid Dispersible Tablets

The optimization of formulation was the next task to formulate an effective rapid dispersible tablet with ideal wetting, dispersion properties to achieve rapid release profile of finished product. On the basis of optimization studies a clear effect of various disintegrants with different granules size fraction was observed on disintegration, dispersion and fineness of dispersion of rapid dispersible tablets. Tablets containing Ac-Di-Sol disintegrated most rapidly with least variability. The dispersion characteristics of tablets containing intra-granular Explotab / Kyron T-314 are less consistent.

The choice of intra-granular disintegrant has a more profound effect on tablet dispersion characteristics than granule size. Where disintegrant efficiency is high, dispersion characteristics may be practically unaffected by changes in granule size. However, as it decreases, granule size becomes more important and disintegration time tends to increase with granule size because size reduction is increasingly dependent on drug dissolution. The release profile of dispersible tablets was evaluated to check the clear impact of disintegrants and granules size fractions. The granules containing Ac-di-sol showed very less overall negligible variation in first five minutes of release profile. The impact of release with change in granules size fraction clearly indicated that the very smaller
granules fractions (500 – 250µm) was retarding the release profile. This may be due to higher compressibility of smaller granules during compression stage.

On the basis of various physical and analytical investigations Ac-di-sol was the most suitable candidate to use as disintegrants in this particular system. The choice of most suitable granules fractions was observed between 500 – 1000µm to formulate rapid dispersible tablets in this particular system.

8.1.3 Dual approach of Technologies in Formulation of Rapid Dispersible Tablets

Application of two different approaches was also an effective tool towards development of rapid dispersible tablets. Formulation of Paracetamol Rapid Dispersible Tablets also formulated with combination of two approaches such as solid dispersion and polymer coating of granules. Paracetamol is a class IV, a low soluble and low permeable drug with bitter taste. Two basic physicochemical properties solubility and permeability directly impact the formulation of drug, low solubility exhibit limited absorption, while low permeability exhibit permeation rate limited absorption (AH Goldberg, 1966). Therefore, ‘Formulation scientist’ basically focuses on these two areas for the better oral bioavailability of drugs by enhancement of solubility and dissolution rate and enhancement of permeability of poorly permeable drugs (GL Amidon et. Al., 1995). Since the formulation was basically developed for the pediatrics so the taste of formulation was also an important factor in development of rapid dispersible tablets of Paracetamol. The solubility of Paracetamol was improved by application of solid dispersion and bitterness of active was masked by application of polymer coating of solid dispersion granules of Paracetamol. The taste was also improved by using sweetener and flavors.

Formulation of Paracetamol was developed and evaluated on the basis of various physical and analytical evaluations; it was found that the prompt release profile of formulation with better organoleptic properties can be easily achieved by simple incorporation of solid dispersion technology with polymer coating of Paracetamol. The combined
approach showed a promising effect in the acceptance of formulation by targeted group of pediatrics and geriatrics patients with better bioavailability of active due to rapid absorption of active into systemic circulation. The comparative evaluation of formulation F-5 and F-6 with other formulations showed a better release profile and acceptable organoleptic properties proved the advantages of combined technology over mono technologies for formulation.

The stability profile of formulation at accelerated conditions such as 40°C temperature and 75% relative humidity for 3 months does not have significant effect on physical and analytical properties of finished product. So the product found stable on specified storage and packaging.

8.1.4 Concept of Fixed Dose Combination in Development of Dispersible Tablets

FDC may be defined as combination of two or more active ingredients in a single dosage form. The current research work was aim to develop a formulation based on fixed dose combination for the effective treatment of migraine. The release profile of Tolfenamic Acid was improved by application of co-micronization, and release profile of Paracetamol was improved by application of solid dispersion method. The taste masking of Paracetamol was done by using polymer coating and finally bitterness of active also masked by using different sweeteners and flavoring agent. Organoleptic evaluations of formulations were evaluated by using human volunteer at the end of formulation.

On the basis of preformulation studies, there were no significant changes observed on FDCs of Tolfenamic Acid and Paracetamol. The disintegration and dispersion properties of finished formulation also fulfill the regulatory requirement (European Pharmacopoeia) in the given formulation.

The usage of Crospovidone showed promising effect on disintegration and dispersion of formulation. The fineness of dispersion also complied as per the specification. The usage of disintegrants improved the release profile of co-micronized Tolfenamic Acid but did not have any impact on solid dispersion of Paracetamol in FDCs. The rapid release of
formulation which was the basic requirement of dispersible tablets was also achieved without any changes in fixed dose combination of Tolfenamic Acid and Paracetamol.

The positive taste results during organoleptic evaluation of FDCs also showing promising acceptance of FDCs in pediatrics and geriatric patient. There was no bitterness of active observed during organoleptic evaluation of tablets. The wetting properties of formulation showed pleasant mouth feeling in case of formulation containing Crospovidone.

The stability profile of formulation at accelerated conditions such as 40°C temperature and 75% relative humidity for 3 months does not have significant effect on physical and analytical properties of finished product. So the product found stable on specified storage and packaging.

8.2 Future Directions

The studies carried out in this thesis have introduced two novel concepts for development of effective rapid dispersible tablets. Successful development of rapid dispersible formulation for treatment of migraine is also a positive indication towards the development of fixed dose combination. Some extended work is underway to explore the clinical performance of these rapid dispersible tablets in terms of patient acceptance, manual handling, mouth feeling upon disintegration and other in vivo data such as sites of absorption, GIT residence time and blood level curve. In term of process development, determination the effect of the soluble diluents and co processed excipients on the release profile kinetics as well as ODT characteristics would be of interest.

The studies carried out in this thesis reveal that further advances in the development of rapid dispersible tablets can be achieved by exploring new materials, innovative formulation processes and novel applications. The future prospects of this dosage form would rely on:

I. Development of a novel moisture protective ODT formulation with promising stability comparable to the conventional compressed tablet and accordingly avoids the need of specialized packaging. This is a challenging task because of the
II. Employment of co-processed excipients and newer concept of manufacturing of rapid dispersible tablets for further improvement of wetting and release profile of tablets. The use of multifunctional excipients in co-processing excipients also minimizing the existing drawbacks of tablets (Saha & Shahiwala, 2009). Basically, the co-processed excipients should dissolve quickly in water to allow easy formulation, possess high wettablility in aqueous medium to allow fast disintegrating in the mouth and form elegant tablet with adequate mechanical strength.

III. There were no any interaction observed during initial development of FDCs of Tolfenamic Acid and Paracetamol. The in vitro in vivo correlation of fixed dose combination of Tolfenamic Acid and Paracetamol needs to be established for further development. Further scope of work is still required to make the formulation of FDCs with smaller size and better taste.

IV. Development of effective method to evaluate wetting properties, disintegration, dispersion and taste is require to correlate the effect of dispersible tablets in the oral cavity and provide reasonable in vitro in vivo correlation (IVIVC). There are several method already studies such as use of analyzer (Abdelhary et al., 2005; El-Arini and Clas, 2002), E-tongue (Murray et al., 2004). But none of them has been officially recognized by the regulatory authorities such as British Pharmacopoeia and European Pharmacopoeia.