7. Summary

Tablet is the most prevailing traditional dosage form for oral administration. It is simple and comfort of self-administration, and available in the accurate dose. Instead of so many advantages there are some disadvantages of solid dosage forms. The pediatric and geriatric patients face problem in consuming the traditional tablets. Hence to resolve this problem the fast dissolved or break up in the mouth tablets to be formulated.

From above reasons the concept of MDT drug delivery system initiated to facilitate the patient in taking easy way as compared to conventional tablets. The mouth dissolving tablets easily disintegrates with saliva on keeping on tongue. The active ingredient present in mouth dissolving tablets is start absorbing from the mouth, pharynx and esophagus as the saliva passes through the stomach. This can increase the bioavailability of mouth dissolving tablets compared to conventional tablet dosage form.

MDT has lot of advantage compared to conventional tablets. Some them are given below:

- Increases the bioavailability
- Side effects can be minimized
- Drug metabolism can be monitored
- Cost effective
- Easy to administered
- Child patient can easily administered it

7.1 Selection of active ingredients

Selection of drug plays chief role before starting the research work. Before finalizing the active ingredients we did literature survey what are the work has been done. From this we can came to know that what new things we can do.
As per data of literature we selected Tolperisone hydrochloride and Celecoxib for further work.

Tolperisone hydrochloride is a centrally acting muscle relaxant having half life of 2 to 3 h, bioavailability of 20% and more stable in acidic than basic media with high solubility in water. Conventional tablet formulations release the active substance in the intestine at pH 4 to 7. In this pH range, tolperisone breaks down into 2-methyl-1-(4-methylphenyl)-propenone (4-MMPOPO) and piperidine. Thus, the patient is exposed to an uncontrollable quantity of 4-MMPOPO. Conventional Tolperisone tablet available in the market are not suitable for acute pain and inflammatory conditions where prompt inception of effect of drug is required. Consequently, an effort was made to enhance the dissolution of Tolperisone through the formulation of mouth-dissolving tablets with appropriate mechanical strength, which would disintegrate in oral cavity, in less than 30 seconds, and would provide an immediate relief from pain due to its faster dissolution in gastrointestinal tract.

The Celecoxib drug is used as nonsteroidal anti-inflammatory. This drug is firstly used as cyclooxygenase-2 inhibitor, in the treatment of osteoarthritis, rheumatoid arthritis, and dysmenorrhea in adult patients. Celecoxib is poor soluble in water & poor absorption in large intestine. The poor water soluble drugs because the rate-limiting step in the process of drug absorption after dissolution. The Celecoxib generally absorbed in stomach. The Conventional NSAID produces ulcer, severe bleeding and perforation in the stomach after long use, but the Celecoxib is free from all these adverse effects. Therefore, an effort was made to enhance the dissolution of Celecoxib by preparing its mouth dissolving tablets; on including superdisintegrates agents namely Crospovidone and Sodium starch glycolate in the diverse ratio.

7.2 Preformulation studies

Preformulation studied has been conducted for Tolperisone and Celecoxib to assess its purity. This study is also applicable in screening the physicochemical characteristics of Tolperisone and Celecoxib.
Firstly preformulation studies of Tolperisone and Celecoxib were done. The following parameters were studied, standard curve of Tolperisone and Celecoxib in pH 6.8 Phosphate Buffer and 0.1 N NaOH were prepared, identification of drug by UV and incompatibility study of drug and excipient using FTIR. Results indicate that Tolperisone and Celecoxib showed good linearity in all the solution systems at a concentration range of 1-10 µg/ml, which follows Beer-Lambert law. The $R^2$ value of both drugs in pH 6.8 phosphate buffers were more nearer to 1 as compared to 0.1 N NaOH solutions. No major deviation in peaks were obtained in IR spectra, hence this manifests that there is no fundamental interaction between drug and other tablet ingredients.

Moreover solubility analysis and melting point of drugs were examined for conformation of purity of active ingredients. The Tolperisone was found to be completely soluble in water, methanol and chloroform, while sparingly soluble in acetone and unsolvable in benzene. The pure drug sample of Celecoxib was found to be liberally soluble in ethanol and unsolvable in water. The melting point of pure Tolperisone and Celecoxib were obtained at 175-178 °C and 158-160 °C respectively.

The above mentioned outcomes indicate that the drugs are suitable to conduct further studies.

### 7.3 Evaluation of pre-compression characteristics of powder blend

Powder blend prepared were investigated for diverse rheological properties like bulk density, tapped density, Hausner’s ratio, angle of repose by using standard procedures. The result of bulk density of Tolperisone range from 0.473 to 0.574 and tapped density from 0.565 to 0.698. Hausner’s ratio was found to be in between 1.14 to 1.23; and Compressibility Index from 12.74 to 19.34. Angle of repose showed good to excellent flow properties of the powdered blend. The result of bulk density of Celecoxib range from 0.473 to 0.483 and tapped density from 0.467 to 0.513. Hausner’s ratio was found to be in between 1.12 to 1.19; and Compressibility Index from 11.39 to 14.09.
Angle of repose showed good to excellent flow properties of the powdered blend.

The findings of pre-compression characteristics of mixture reveal the suitability of powder for the formulation of tablets. The pre-compression investigation indicates that the values are within limit.

### 7.4 Evaluation of mouth dissolving tablet of Tolperisone and Celecoxib

Tablets can be prepared by direct compress and wet granulation method, but here we applied direction compression method for the preparation of MDT. This method is more suitable and easier than the wet granulation methods.

Following are the advantages over wet granulation method:

- Less time consuming
- Cost effective
- Simple to operate, not tedious
- Minimum wastage of formulation
- Hardening issues can be minimize

Tablets of Tolperisone and Celecoxib were formulated by direct compression method. All the formulation ingredients were weighed accordingly and mixed in a mortar and pestle. This powder blend was then allowed to dry for few moments and then again mixed well and crossed through sieve no 60. Then mixture was used for further processing.

The formulated tablets were assessed for their thickness, hardness, weight variation, friability, assay, wetting time, water absorption ratio, \textit{in-vitro} disintegration time and dissolution study. All the formulations of prepared tablets were subjected to \textit{in-vitro} release studies. These investigations were continue out by employing dissolution apparatus, pH 6.8 phosphate buffers,
and the outcomes obtaining *in-vitro* release studies were plotted in different model.

The thickness of all formulations of Tolperisone and Celecoxib were noted to be between 3.21 to 3.62 and 2.25 to 2.84 respectively. The tablet weights of all baxes of Tolperisone and Celecoxib were found with in recommended USP limits, between 305 ± 1 mg and 218 ± 1 mg, respectively. The hardness and friability of tablets of all batches of Tolperisone and Celecoxib were in acceptable limits. The uniformity content of active ingredients in both tablets was under USP limit.

The thickness, hardness and friability of tablets were under limit and it can produce desirable MDT.

The wetting time of Tolperisone and Celecoxib tablets were 17.79 to 35.07 seconds and 13.25 to 27.38 seconds respectively. The water absorption ratio of Tolperisone and Celecoxib tablets were 39.24 to 73.38 seconds and 84.73 to 40.62 seconds respectively. The disintegration time of Tolperisone and Celecoxib tablets were 38.21 to 22.36 seconds and 18.16 to 31.84 seconds, respectively. From results it has been observed that T7 and C7 formulation exhibited excellent wetting time, water absorption ration and disintegration time as compared to other formulations.

The above findings of formulated tablets indicate that T7 and C7 were excellent formulation compared to other formulations.

### 7.5 *In vitro* drug release studies

Results register that 78 to 100% of drug release from various formulations from Tolperisone mouth dissolving tablets. Among all the formulations, T7 showed 98.16% drug release from the tablet at 14 minutes. Results of *in vitro* drug release of Celecoxib from mouth dissolving tablets revealed that 76 to 100% of drug release from various formulations. The formulation C7 exhibited 98.89% of Celecoxib released in 14 minutes from tablets. The dissolution rate was found to increase linearly with increase in the concentration of
superdisintegrant. Mechanism it followed was wicking and swelling with minimum gelling. Hence T7 and C7 were selected for further studies.

The *in vitro* studies of tablets of T7 and C7 support the agreement of post compression studies.

### 7.6 Kinetics of *in vitro* drug release

The formulations of Tolperisone tablets were subjected to four model fitting analysis namely, zero order, first order, Higuchi and Korsmeyer-peppas model. Results indicate that all the formulations follow the higuchi order kinetics as the co-efficient of regression ($R^2$) was more near to unity as compared to the regression value of zero order and first order model. Among all the formulations it was observed that $R^2$ value of formulation T7 was more near to one than formulations. On the basis of this parameter, T7 was selected for further study.

Results exhibited that all the formulations follow the first order kinetics as the co-efficient of regression ($R^2$) was more near to unity as compared to the regression value of zero order and Higuchi model. Among all the formulations it was observed that $R^2$ value of formulation C7 was more near to one than formulations. On the basis of this parameter, C7 was selected for further study. The values of $n$ in Korsmeyer-peppas model suggested that all formulations of Tolperisone and Celecoxib tablets follow Non Fickian Anamolous.

### 7.7 $3^2$ full factorial design

The amounts of the superdisintegrants (Crospovidone, $X_1$ and Sodium starch glycolate, $X_2$) were chosen as independent variables in a $3^2$ full factorial design. It is applied to optimize the ingredient used in formulation of MDT. The factorial design is suitable to check the minimum quantity required to formulate best formulation among the prepared tablets.

The variables for factorial design considered on the basis of performance in MDTs formulation. The data of pre-compression and post compression of
MDTS indicates that superdisintegrants play vital role in disintegration of tablets.

Following parameter are observed on changing the concentration of Crospovidone and Sodium starch glycolate in the tablets.

- On increasing the concentration of Crospovidone and Sodium starch glycolate it reduced the wetting time of MDTs
- On increasing the concentration of Crospovidone and Sodium starch glycolate it enhanced the water absorption ratio of MDTs
- On increasing the concentration of Crospovidone and Sodium starch glycolate it reduced the disintegration time of MDTs

Hence it has concluded that on slight changing the concentration of Crospovidone and Sodium starch glycolate, it can produce effective wetting time, water absorption ratio and disintegration time of MDTs.

**7.8 Evaluation of factorial Design mouth dissolving tablet of Tolperisone and Celecoxib**

The friability of $3^2$ full factorial design tablets of all batches of Tolperisone and Celecoxib were in acceptable limits. The uniformity content of active ingredients in both tablets was under USP limit.

The wetting time of factorial tablets of Tolperisone and Celecoxib tablets were 17.02 to 20.57 seconds and 17.58 to 21.41 seconds respectively. The water absorption ratio of Tolperisone and Celecoxib tablets were 68.87 to 75.31 seconds and 75.62 to 81.25 seconds respectively. The disintegration time of factorial tablets of Tolperisone and Celecoxib tablets were 21.79 to 25.34 seconds and 22.18 to 18.46 seconds, respectively. From results it has been observed that T7 and C7 formulation exhibited excellent wetting time, water absorption ration and disintegration time as compared to other formulations. The results reveal that TC7 and CC7 formulation exhibited excellent wetting time, water absorption ration and disintegration time as compared to other formulations.
7.9 *In vitro* drug release studies of factorial design tablets

Results display that 97.61 to 100% of drug release from various formulations from factorial tablets of Tolperisone mouth dissolving tablets. Among all the formulations, TC7 showed 100% drug release from the tablet at 14 minutes. Results of *in vitro* drug release of Celecoxib from mouth dissolving tablets exposed that 97.24 to 100% of drug release from various formulations. The formulation CC7 exhibited 100% of Celecoxib released in 14 minutes from tablets. The dissolution rate was found to enhance linearly with proliferate in the concentration of superdisintegrant. Mechanism it followed was wicking and swelling with minimum gelling. Hence TC7 and CC7 were selected for further studies. From the result, it was noticed that on enhancing the concentration of Sodium starch glycolate disintegrates in formulation it decreases the release of drug. This might be due to gelling character of sodium starch glycolate. Hence the formulation TC7 and CC7 considered best among other formulations.

7.10 Kinetics of *in vitro* drug release of factorial design tablets

Results indicate that all the formulations of factorial tablets of Tolperisone and Celecoxib follow the higuchi order kinetics as the co-efficient of regression ($R^2$) was more near to unity as compared to the regression value of zero order and first order model. Among all the formulations it was observed that $R^2$ value of formulation TC7 and CC7 was more near to one than formulations. On the basis of this parameter, TC7 and CC7 were selected for further study. The values of $n$ in Korsmeyer-peppas model suggested that all formulations of Tolperisone and Celecoxib tablets follow Non Fickian Anamolous.

7.11 Conclusion

It was deduced that MDTs of Tolperisone and Celecoxib prosperously formulated by direct compression method. The superdisintegrants were used in formulation to ameliorate the disintegration of tablets. It produces better patient compliance and effective therapy of tablets. Also the bitter drug can be easily formulated as mouth dissolving tablets by masking their taste using aspartame as taste masking agent. It was also found that the
superdisintegrants are effective at an optimum concentration, on increasing the ratio of Crospovidone and Sodium starch glycolate concentration above their optimum concentration this enhance the gelling effects of formulation. The formulation TC7 and CC7 exhibited better results as compared to other formulations. Further these formulations can be select for *in vivo* study.