5. CONCLUSION

- The objectives of the thesis is to develop and assess chronomodulated formulation, combination of one dosage form having two releases immediate and sustained release core are to delivered a quick and steady of drug in the GIT, which allowed for the sustained absorption and maintained at constant plasma concentrations, which is having a narrow therapeutic range. The reduced plasma fluctuations level, that will decrease the incidence and severity of associated side effects such as drowsiness, ataxia, diplopia, since these side effects are dose-dependent.
- The clinically use for chronomodulated drug delivery system to enhance through a combination of improving patient compliance by reducing the dosing frequency by anti epileptic therapy. The optimizing drug delivery through the sustained and immediate release of CBZ to cure epileptic seizure.
- Due to Carbamazepine is poor solubility and high permeability, although right choice is selected for 1 % SLS is required to enhance the solubility. As per preformulation study among all formulations, from F10 shown very good results for the above evaluation parameters. Compressibility index of all the formulations was found in between 12 to 15, indicates good compressibility index. Angle of repose of all formulations are found to be < 30° C, declares that all the formulations are possessing excellent flow properties. and Hausner’s ratio of all formulations was originated to be 1.0 to 1.2, which satisfies the limits of compressibility.
- DSC thermograms revealing thermal shifts for CBZ, when it was assessed by combination with the polymers used in formulation of tablets. Carbamazepine was obtained at 194°C equivalent to the melting point, but the optimized the formulation was a minor change in peak temperature as 193.3 °C was observed, which might be due to reduction of the integrity level and interaction with excipients. Furthermore, XRD studies was indicated that CBZ didn’t show any polymorphic transitions during mixing, granulation and tableting and therefore, it was concluded that drug release rates dosage form design and composition rather than transformation to a low solubility polymorph during production.
In FTIR studies, same peaks of drug and physical mixture i.e. (drug and all excipients) were not showing any new peak in spectrum, so it indicates the stable nature of drug. Hence it found to be indicated that there is no interaction indicated between the carbamazepine and excipients like polymers.

The design of chronotherapeutic drug delivery of carbamazepine, having two layer sustained release 200 mg core tablets & immediate release 200mg granules also formulated by wet granulation techniques. Initially prepared by sustained release tablet, in that again punch the immediate release granules on that prepared by inlay tablet, it is of sustained inner core tablet and outer immediate release tablet.

The weight variation of inlay carbamazepine tablet is in the USP limit is ±5 %, hardness is ±5 % and friability is less than 1 %.

In vitro dissolution test carried by using USP Type-II dissolution apparatus was to be suitable for drug release profiles of the immediate release layer and after that sustained release core tablet. It is probably that test tablets exposed to fresh dissolution medium, at a predetermined lag time, prohibited for the formation of diffusion conditions and enabled greater bias by different composition. In addition to the exposure of dosage forms to a range of media of different pH like 1.2 & 6.8 was considered suitable and more significant for assessing dosage form performance than exposure to pH 6.8 dissolution medium.

Outermost comprised of quick or first releasing layer (immediate) for a period of up to 1 hr and inner most core has meant for sustained the drug release for time period of 10 hours. Sodium starch glycolate was selected as super disintegrating agent, ranging from 6 to 10.5 mg in outer quick disintegrating layer. Mean while the amount of binding agent, Povidone K-30 remained to be constant in all batches. Micro crystalline cellulose (AVICEL-101) was selected as diluent ranging from 10.5 to 15 mg in all batches. In-vitro release pattern for outer layer was studied in USP dissolution type-II (Paddle type) for period of 2 hours in 0.1 N HCl. During initial half an hour 55 to 90% of drugs were released and at the end of two hour maximum of 99% and least of 68% of drug was released for formulation F10 and F3 respectively. From F4 a sudden release of 10% was observed, which may be the bursting of outermost layer of tablet. Result showed as the amount of SSG increased, the quicker the drug released. Whereas in F3 and F9
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Contradictory to the above mentioned result observed. This may be the possible influence of Avicel-101. Because, researches already proved that Avicel has both the property of binding and disintegrating agent.

- Further in-vitro release was studied in phosphate buffer pH 6.8 till to end i.e 10 hours. The inner portion contained di calcium phosphate as diluents, controlling release polymers like HPMC K4M, HPMC K100M and EC were selected at variable proportions. A quicker and maximum of 102% of drug release was observed in 7th hour for F3 and least 85% of drug release was in F8 till to end of 10th hours. A comparison was made between F4 and F5, 100% drug was released in F4 but in F5 only 90% released was observed. Another result was noticed that in F7 as drug released 88%, but in F8 only 85% drug released, though lack of HPMC K100M in latter formulation. This may be the possible reason that HPMC K4M has better rate retarding property than K100M. Data showed the quicker drug releases were observed in HPMC K4M and K100M. But in combination with EC slower drug release were noticed, as EC is hydrophobic in nature and difficult to form channel through inner core. Whereas, in case of hydrophilic polymers (HPMC K4M and K100M), they draw surrounding medium and forms channel. Among all formulation F10 was selected as optimized batch, as 99% of drug was released at 2nd hour and followed by 101% at the end of 10 hours.

- The effect for the carbamazepine particle size on release concert from these dosage forms was also ascertained and further the optimized of formulations was achieved by use of the fine and coarse grade CBZ in different combinations of polymers. Different ratios of the different particle size grades of CBZ, yielded more defined drug release rate data that could be modified depending on the content of the individual particle size grade of CBZ. The effects of tablet components such as the type, grade and proportion of the polymers used during formulation, significantly influenced drug release rates from these matrix tablets where the use of a lower viscosity grade HPMC and EC revealed a greater rate and extent of CBZ drug release from tablets. The incorporation of a surfactant SLS in the formulation composition even at 1% concentrations further enhanced the rate and extent of drug release from these dosage forms.

- The Kinetic release of carbamazepine chrono tablet during study, all the formulations obeyed either zero order or Higuchi pattern. The greatest fit with higher
correlation coefficient ($r^2 > 0.99$) was initiating with Zero order’s kinetic release model for F10. The mechanism of drug release were fitted by Korsmeyer–Peppas model. For the regression analysis was found values of regression coefficient ($r^2$) were ranged from 0.78 to 0.93 for different formulations and slope of $0.43 < n < 0.54$. Hence, it can be inferred that the release was based on Fickian diffusion transport. On the source of the above results, F10 was selected as a promising formulation. The in-vivo test of anticonvulsant activity was performed using maximal electroshock seizure test and PTZ induced convulsion The MES test to identify drugs which prevent seizure which is identical to generalized tonic-clonic seizures in humans. There are for stages of convulsion flexion, extensor clonus and stupor. There are two treatment done by first one is control and second one is different extract like petroleum ether, chloroform, methanolic and aqueous extract as well as carbamazepine taken as consideration. Among all these carbamazepine having good accuracy result due to seizure latency, seizure severity, seizure duration is less. There was decreased time for onset of convulsions in groups treated with carbamazepine, medium & high dose of different extract in comparison with control animals, which reduce the possibility and frequency of unwanted side effects that would be reduce patient compliance.

➢ The invitro & in vivo correlation for the optimized formulation was preserved under accelerated conditions showed the greatest increase in moisture content, drug content & dissolution of tablets. It is stored under ambient conditions had a moisture content well within specification. The stability study depends on humidity and temperature. The relative Humidity 25 ± 2°C/60 ± 5%, 30 ± 2°C/65 ± 5% RH, and 40 ± 2°C/75 ± 5% RH respectively. Twenty tablets of the optimized formulation batch was packed by aluminum blister and placed in humidity chamber. There was no significance change in crushing strength and drug assay at a regular interval of 3rd, 6th & 12th months during the study of one year. The formulation F10 was stable after one year of stability period.

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