2.0 REVIEW OF LITERATURE

1. **Raju Manda et al** (2010), have formulated and *In-Vitro* evaluated of sustained release matrix tablets of Aceclofenac using different natural polymers such as Guargum, Xanthan gum, Chitosan in various proportions as release controlling factor by direct compression method. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and hausner ratio etc. The *in vitro* dissolution study was carried out for 11 hrs using USP 1 Basket-type dissolution apparatus in 0.1N HCl for first 2 hr and phosphate buffer pH 7.4 for 9 hr. The powder blend showed satisfactory flow properties. All the tablets complied with pharmacopoeial specifications. The *in vitro* release study shows that only F9 formulation was releases the drug in a sustained manner for 11 hr.

2. **Sivakumar T et al** (2010), have designed and characterized of Diclofenac sodium tablets containing *Mangifera indica* resin as release retardant and various concentrations of resin ranging from 4 to 6% w/w used to prepare matrix tablets by Wet granulation technique. The resin of *Mangifera indica* exhibited excellent retarding effect on drug release even at its low concentrations (4% w/w). Among the formulation studied, formulation F2 and F3 showed release of drug more than 12 hr. The kinetics of drug release from the resin matrix predominantly follows Higuchi patterns followed by first order, Peppas and then zero order. According to Peppas model, the mechanism of diffusion was found to be non-Fickian. The FT-IR spectral analysis shows drug is compatible with the polymer.

3. **Velmurugan S et al** (2010), prepared buccoadhesive tablets of piroxicam by using HPMC K4M and carbopol 934 as mucoadhesive polymers. The formulations were tested for *in-vitro* drug release, bioadhesive strength, moisture absorption, residence T and drug permeation through porcine buccal mucosa. Optimized formulation H3 showed maximum release of the drug (97.67±0.41) with the peppas model release profile and permeated 26.52±0.19 of the drug through porcine buccal membrane. H3 formulation
showed 12.5gm of mucoadhesive strength, the FTIR results showed no evidence of interaction between the drug and polymers. The results indicated that suitable bioadhesive buccal tablets with desired permeability could be prepared.

4. **Ghosh S et al**\(^{10}\) (2009), have prepared and evaluated of Aceclofenac sustained release formulation compared with marketed product. Matrix tablets of Aceclofenac were prepared, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose by wet granulation method and subjected to *in vitro* drug release studies. The results of the *in vitro* studies in pH 7.5 phosphate buffer medium showed that F7 tablets provided controlled release comparable with marketed sustained release formulation (Aeroff-SR tablets).

5. **Patel B et al**\(^{11}\) (2009), they were evaluated of tamarind seed polysaccharide as a mucoadhesive and sustained release component of nifedipine mucoadhesive tablet and comparison with HPMC and sodium CMC, Best mucoadhesive performance and in vitro drug release profile were exhibited by the tablet containing carbopol and TSP in the ratio of 1:1. This formulation was more comfortable to the user to do less erosion, faster hydration rate, and optimum pH of surrounding medium.

6. **Jha K et al**\(^{12}\) (2009), have formulated and evaluated of sustained release Metoprolol succinate tablet using hydrophilic gums as release modifiers such as karaya gum (KG) and xanthan gum (XG) in the concentration of 15%, 20% and 25% alone and in combination of 2:8. Matrix tablets were prepared by wet granulation method. Among the formulation studied, formulation F8 showed 99.24% release of drug for 12hr. The release kinetics revealed that all the formulation follows zero order drug release with release exponent value (n) 0.7656 and having good stability as per ICH guidelines.

7. **Tadros MI et al**\(^{13}\) (2008), have designed and carried out *in vitro/in vivo* evaluation of novel Nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer Chitosan (CH)/hyaluronate sodium (HA),
pectin (PE) or alginate sodium (AL) interpolymer complexes (IPC's) were prepared. The optimum IPC's (CH: HA, 40:60), (CH: PE, 30:70) and (CH:AL, 20:80) were characterized by Fourier transform infrared spectroscopy. Nicorandil matrix tablets were prepared using the optimum IPC's, alone or in combination with Imwitor 900 K. The *in vitro* drug release studies revealed that formula F11 (CH: AL, 20:80) IPC : Imwitor_900 K, 3:1) could extend drug release for more than 8 hr. Most formulae exhibited non-Fickian diffusion drug release profiles.

8. **Kulkarni RV *et al* [14] (2008),** have developed and evaluated of xyloglucan matrix tablets containing naproxen using xyloglucan (XGL), HPMC, cellulose acetate phthalate (CAP) and ethyl cellulose (EC) were prepared by conventional wet granulation technique and concluded that, the tablets containing XGL in combination with CAP has released 98.08% with extended over a period of 10 hr of dissolution study, hence it is a good combination for the controlled release of drugs.

9. **Patil UK *et al* [15] (2008),** were prepared and evaluated of SR matrix tablet of Furosemide using natural polymers and the tablets were prepared by direct compression technique. All formulations showed very low drug release in 0.1N HCl (pH 1.2). This was due to the low solubility of Furosemide at pH 1.2. Sustained, but complete drug release was displayed by all formulations in phosphate buffer pH 7.4. Thus it can be concluded, that drug dissolution was a function of drug solubility, at various pH ranges. Indeed, pH dependent solubility of Furosemide is well known. A better controlled drug release (80.74%) was obtained with the matrix tablet (G4) made-up of the guar gum than with the pectin and xanthan gum. It is cleared through the dissolution profile of furosemide from matrix tablets prepared using different natural polymers were retarded approx 15 hr.

10. **Ganesan V *et al* [16] (2008),** have designed and evaluated of matrix tablets of Ambroxol HCl using Guar gum, the tablets were prepared by wet granulation method using various viscosity grades of guar gum in three proportions. Showed that the results of dissolution studies indicated that formulation F-IX is the most successful formulation of the study.
and exhibited satisfactory drug release in the initial hrs and the total release pattern was very close to the theoretical release profile as well as marketed sustained release ambroxol hydrochloride tablets.

11. **Punna Rao Ravi et al** (2008), were prepared controlled release matrix tablets of zidovudine using different proportions and different viscosity grades of hydroxypropyl methylcellulose. They studied the effect of various formulation factors like polymer proportion, polymer viscosity and compression force on the *in vitro* release of drug. In vitro release studies were carried out using United States Pharmacopeia (USP) type 1 apparatus (basket method). They concluded that the controlled release matrix tablets of zidovudine conforming to good quality were prepared using HPMC by wet granulation method. Release rate of the drug from the matrix tablets was dependent on proportion as well as viscosity of HPMC used. The effect of compression force on the drug release was more pronounced at lesser compression forces than at higher compression forces. Drug release was found to follow non-Fickian or anomalous release mechanism. The designed CR matrix tablets of zidovudine (formulations H4-1, H4-2 and H15-1), which release 17-25% of drug in first hour and extend the release up to 16-20 h, can overcome the disadvantages associated with conventional tablet formulations of zidovudine.

12. **Kyeo-Re lee et al** (2008), prepared controlled release matrix tablets containing Felodipine using poly vinyl pyrrolidone (PVP), poloxamer, HPMC(hydroxyl propyl methyl cellulose), Poly ethylene glycol 8000, carbopol 971. They observed that the interaction between poloxamer & carbopol further retarded dissolution of the tablets matrix. The release of felodipine from tablets was almost zero order when the content of the carbopol was increased to 5 to 10%. Felodipine was solubilized the tablets matrix due to a high local concentration of poloxamer and the solubilized felodipine slowly diffused out of the matrix.

13. **Nagaswamy D et al** (2008), were prepared sustained release matrix tablets of theopylline using ethyl cellulose. A wet granulation technique was employed to prepare
matrix tablets by utilizing drug and different concentration of polymer (10, 20, 30, 40, & 50%) were included in the formulation containing 200 mg of theophylline. The prepared tablets were evaluated for various physicochemical parameters by official procedures. The in vitro release study of matrix tablets were carried out in phosphate buffers pH 1.2 or 6.8 for 12 hrs and the results showed that the formulation and evaluation of sustained release matrix tablets containing theophylline was found to be potential, cost effective and satisfactory in vitro release studies. In turn, it may enable to drug release in a sustained manner for prolonged time and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance.

14. Derle DV et al\textsuperscript{20} (2008), were prepared sustained release matrix tablets of Tizanidine Hydrochloride using xanthan gum and guar gum. They have studied the effect of matrix former xanthan gum and guar gum separately. Tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, in vitro dissolution and swelling index. They have observed that the minimum quantity of xanthan gum and guar gum required to prepare sustained release matrix tablets of tizanidine hydrochloride is 12% and 6% respectively to retard the drug release up to 12h. Kinetic studies revealed that drug follows diffusion controlled mechanism and stability studies shown that there was no significant change in hardness, friability, and drug content of selected formulations. They concluded that xanthan gum and guar gum can be used as an effective matrix former to retard the release of tizanidine hydrochloride for extended period of time.

15. Amelia A et al\textsuperscript{21} (2007), have developed and characterized controlled release matrix tablets of diclofenac sodium and chondroitin sulphate using hydroxy propyl methyl cellulose with different concentrations. They developed matrix tablets by wet granulation technique to contain 100 mg of Diclofenac sodium and 400 mg of chondroitin sulphate. They concluded that diclofenac sodium and chondroitin sulphate can be co-administered in the form of a single controlled release matrix tablet. It is evident that the investigated
controlled release matrix of HPMC 40% concentration was capable of prolonging the release of both drugs simultaneously for 9 Hrs. The mechanism of drug release was observed to be following Korsameyer-peppas model and zero-order kinetics for diclofenac sodium and chondroitin sulphate, respectively.

16. Hamdy A et al\textsuperscript{22} (2007), have designed and developed controlled release matrix tablets of baclofen studied using methylcellulose (MC), sodium alginate (Alg), and sodium carboxy methylcellulose (CMC). The results demonstrated that the release of baclofen from all prepared matrix tablet formulations was generally sustained. The drug release from matrix tablets containing methylcellulose and sodium alginate was non-Fickian. In addition, in vitro release profiles of the drug from the above-mentioned matrix tablet formulations did not alter significantly upon storage at ambient conditions. Therefore, these polymers can be used to modify release rates of baclofen in hydrophilic matrix tablets.

17. Punna Rao Ravi et al\textsuperscript{23} (2007), were developed oral controlled release tablets of lamivudine. Using HPMC as the retardant polymer and studied the effects of various formulation factors such as polymer proportion, polymer viscosity, and compression force on the in vitro release of the drug. In vitro releases were performed using US pharmacopeia type 1 apparatus (basket method). They have concluded that controlled release matrix tablets of lamivudine conforming to good quality were prepared using HPMC by the wet granulation method. Release rate of the drug from the matrix tablets was dependent on the proportion as well as the viscosity of HPMC used. The effect of compression force on the drug release was more pronounced at lower compression force then at higher concentration forces. Drug release was found to follow a non- Fickian or anomalous release mechanism. The designed controlled release matrix tablets of lamivudine, which release 20% to 30% of drug in the first hour and extend the release up to 16 to 20 hours, can overcome the disadvantages associated with conventional tablet formulation of lamivudine.
18. **Gohel MC et al**\(^{24}\) (2007), formulated and optimized the isoniazid directly compressed modified release matrix tablet using low-viscosity grade HPMC, medium-viscosity grade HPMC, and high-viscosity grade HPMC. The in-vitro release study reveals that the rate was strongly influenced by the type of polymer and concentration of polymer. The optimized formulation followed the weibull model. The use of simplified optimization methodology is demonstrated to evolve unified mathematical model.

19. **Yeole PG et al**\(^{25}\) (2006), studied the release of drug from Xanthan gum based sustained release matrix tablets of diclofenac sodium by using xanthan gum, polyethylene glycol (PEG) 6000 and concluded that xanthan gum can be used as an effective matrix former, to retard the release of diclofenac sodium for extended period of T.

20. **Varshosaz J et al**\(^{26}\) (2006), have Used of hydrophilic natural gums in formulation of sustained release matrix tablets of tramadol HCl were produced by direct compression method. They have concluded that guar gum alone cannot efficiently control drug release, while xanthan gum and all combination of each natural gum with HPMC could retard tramadol HCl release. However, according to the similarity factor (f2), pure HPMC and H8G2 were the most similar formulations to Topologic-LP as the reference standard.

21. **Senapati MK et al**\(^{27}\) (2006), they were studied *In vitro* release characteristics of matrix tablets study of karaya gum and guar gum as release modulators, the tablets were evaluated for physical characteristics like hardness, weight variation, friability, swelling index and drug content. A combination of karaya gum and guar gum exhibited more sustained release than individual gum.

22. **Nerkur J et al**\(^{28}\) (2005), have fabricated controlled release matrix tablets of ibuprofen using cellulose ethers and carragenans: effect of formulation factors on dissolution rates. Matrix tablets were prepared by using Polymer blends containing carrageenans or cellulose ethers by direct compression technique, concluded that Matrix tablets containing a blend of carrageenans and cellulose ethers successfully sustained the release
of ibuprofen for a period of 10–12 hr. Ibuprofen was predominantly released by anomalous (non-Fickian) mechanism that is diffusion through the honeycomb network and polymer relaxation.

23. **Saleh M et al** (2005), prepared oral controlled release matrix tablets of diltiazem hydrochloride using various viscosity grades of guar gum in two proportions. The tablets where prepared by wet granulation method. They concluded that the results of in-vitro release studies in stimulated GI fluids and colonic fluids showed that matrix tablet containing 50%w/w of guar gum was able to control the release water soluble diltiazem hydrochloride. The in vivo pharmacokinetics evaluation of tablets in human volunteers showed a slow and proelongs release of diltiazem Hydrochloride indicating the potential for clinical studies.

24. **Emami J et al** (2004), formulated sustained release lithium carbonate(LC) matrix tablets and studied influence of hydrophilic materials by using different ratios of polymer including carbopol (cp), Sodium CMC, HPMC and concluded that release of LC from all formulated sustained matrix tablets were generally sustained. Na CMC, CP, and HPMC can, therefore, be used to modify release rates of LC in hydrophilic matrix tablets.

25. **Hajare AA et al** (2004), have designed and evaluated sustained release tablets of diltiazem HCl by using guar gum, sodium CMC and HPMC polymer, various physical characteristics drug-polymer interactions *in-vitro* drug release and stability were evaluated. The prepared tablets were found to have good physical integrity free from drug polymer interactions and have good stability. The drug release was found to follow zero order.

26. **Shan-yang Lin et al** (2004), have prepared controlled disintegration press-coated tablets using spray dried lactose, hydroxyl propyl methyl cellulose and the tablets developed by means of direct compression to achieve the time-controlled disintegrating
or rupturing function with distinct predetermined lag time. This press-coated tablets containing diclofenac sodium in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of micronized ethyl cellulose powder and hydrophilic excipients such as spray-dried lactose or Hydroxypropyl methyl cellulose. They have concluded that the time lag was controllable by varying the composition of the outer coating layer. They observe that the time lag of the press-coated tablet can be suitably modulated by formulating the outer shell with micronized ethyl cellulose and spray dried lactose or hydroxyl propyl methyl cellulose.

27. Crowley MM et al\textsuperscript{33} (2004), studied physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion.

28. Koesterc LS et al\textsuperscript{34} (2004), performed mathematical evaluation of in vitro release profiles of hydroxypropylmethylcellulose matrix tablets containing carbamazepine associated to β-cyclodextrin. The release kinetics of carbamazepine (CBZ) either complexed or physically mixed with β-cyclodextrin (βCD) from hydroxypropylmethylcellulose (HPMC) matrix tablets was investigated using different mathematical equations.

29. Raghuram Reddy et al\textsuperscript{35} (2003), prepared sustained release matrix tablets of nicorandil using HPMC, Eudragit RL 100 and RS 100 and ethyl cellulose, polyvinyl pyrrolidine. The tablets were prepared by wet granulation method the results showed that the hydrophilic matrix of HPMC alone could not control the nicorandil release effectively for 24 hr. They observed that the results from matrix tablets prepared with HPMC and granulating agent of hydrophobic polymer (ethyl cellulose 4%w/v) is a better system for once daily sustained release of a highly water soluble drug like nicorandil. Formulations exhibited diffusion dominated drug release.

30. Sandip BT et al\textsuperscript{36} (2003), they have prepared controlled release matrix tablets of Tramadol Hydrochloride using Hydrogenated vegetable oil, hydroxy propyl methyl
cellulose, Ethyl cellulose. They studied the effect of concentration of Hydrophilic (Hydroxy propyl methyl cellulose) and Hydrophobic polymers (Hydrogenated castor oil, Ethyl cellulose) on the release rate of tramadol was studied. Hydrophilic matrix tablets were prepared by wet granulation technique, while Hydrophobic matrix were prepared by melt granulation technique and In-vitro dissolution studies were performed using united states pharmacopeia apparatus type II. They have concluded that hydrophilic matrix of Hydroxy propyl methyl cellulose could not control the tramadol release effectively for more than 12 hours. It is evident from the result that a hydrophobic matrix prepared by HCO is a better system for controlled delivery of a highly water-soluble drug like. Tramadol hydrochloride. The release of coating with water-soluble excipients (HPMC 6 cps and lactose) proved to be useful as a functional coating to control the drug release along with masking the bitter taste of the drug.

31. **Sumathi S et al**\(^\text{37}\) (2002), have studied release behaviour of drugs from TSP tablets with water soluble and insoluble model drug such as acetoaminophen, caffeine, theophylline, salicylic acid and indomethacin. They have concluded that the mechanism of release of soluble drugs was found to be anomalous. The insoluble drug showed near case II or zero order release mechanism. The rate of release was in the decreasing order of caffeine, acetoaminophen, theophylline, salicylic acid and indomethacin.

32. **Murali Mohan Babu GV et al**\(^\text{38}\) (2002), have developed controlled release formulation of flurbiprofen: \textit{in-vitro/ in-vivo} correlation flurbiprofen-gum karaya matrices showed first order release kinetics following super case II transport were as matrices with both of the co-excipient followed first order kinetics with anomalous diffusion release.

33. **Sanchez-Lafuente CS et al**\(^\text{39}\) (2002), developed sustained release matrix tablets of didanosine containing methacrylic and ethylcellulose polymers. The results showed that less than 50% of drug release was seen after 6hr. This showed the suitability of Eudragit–Ethocel mixtures as matrix-forming material for didanosine sustained release formulations.
34. **Sanchez-Lafuente CS et al** \(^\text{40}\) (2002), perform optimization of formulation variables using statistical experimental design of didanosine extended-release matrix tablets. The experimental values obtained from the optimized formulation highly agreed with the predicted values. The results demonstrated the reliability of the model in the preparation of extended-release matrix tablets with predictable drug release profiles.

35. **Sanchez-Lafuente CS et al** \(^\text{41}\) (2002), studied the influence over the behavior of didanosine (ddl) inert matrix system using eudragit RS-PM and ethocel 100 polymer. The in vitro release of ddl matrices was studied at pH 7.4, because of the instability of didanosine at pH values lower than 3 units. A significant reduction in the release rate of drug from both didanosine controlled release systems was found.

36. **Betageri GV et al** \(^\text{42}\) (2001), prepared sustained-release bioadhesive tablet formulation of didanosine. Tablet formulations with Polyox WSRN-303 (10%) and Methocel K4M (30%) showed 93 and 90% drug release, respectively, after 12 h. The drug release was found to be linear when fitted in the Higuchi equation (square-root time equation), suggesting zero-order release.

37. **Nath BS et al** \(^\text{43}\) (2000), formulated and evaluated of sustained release dosage form of theophylline using combined hydrophobic and hydrophilic matrix. The *in-vitro* release data showed that 30% w/w total matrix component gave extended release of theophylline for more than 8 hr. Analysis of drug release rate from the matrix system indicated that the drug was released by anomalous diffusion obeying first order rate kinetics.

38. **Dale L et al** \(^\text{44}\) (2000), were prepared compressed xanthum and karaya gum matrices: hydration, erosion and drug release mechanisms. Directly compressed matrices were produced containing either xanthan gum or karaya gum as a release controlling agent. These swellable hydrophilic natural gums were used to control the release of varying proportions of 2 model drugs, caffeine and diclofenac sodium, which have different solubilities in aqueous medium. Gum erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method) at two agitation speeds.
Ph.D. Synopsis

Xanthan gum displayed a high degree of swelling due to water uptake and small degree of erosion due to polymer relaxation. Neither agitation speed nor drug solubility had any significant effect on water uptake, but matrices with the lower proportion of gum produced a lesser degree of hydration. In contrast karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed. Drug release from xanthan and karaya gum matrices dependent on agitation speed, solubility and proportion of drug. Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices.

39. Paolo Giunchedi et al\textsuperscript{45} (2000), prepared Alginates compressed matrices as a prolonged drug delivery system using sodium alginate (Alg) and HPMC. They investigated the use of Sodium alginate for the preparation hydrophilic matrix tablets intended for prolong drug release using ketoprofen as a model drug. The matrix tablets were prepared by direct compression using sodium alginate, calcium gluconate and Hydroxy propyl methyl cellulose in different combination & ratios. They have concluded that sodium alginate can be used to modify release rates in hydrophilic matrix tablets prepared by direct compression. The results showed that the sustained release effects of sodium alginate and hydroxypropylmethylcellulose were the best among the formulations studied. They behave as zero-order release systems.

40. Torrado S et al\textsuperscript{46} (1996), studied effect of drug release rate on bioavailability of different asprin (ASA) tablets. ASA pellets coated by Eudragit RS or L were tableted with different proportions of microcrystalline cellulose 0 or 25% (W/W). The bioavailability of six different formulations were assayed in volunteer by urine excretion data. Bioavailability was related to the dissolution release rate. Formulations with faster drug release rate showed higher bioavailability. Only the slowest formulations had a reduced bioavailability.

41. Knupp CA et al\textsuperscript{47} (1993), studied the effect of time of food administration on the bioavailability of didanosine from a chewable tablet formulation. Based on the data from
this study, it is recommended that didanosine be administered 30 minutes to 1 hour before a meal, but not within 2 hours after a meal.

42. **Basak SC et al**\(^{48}\), formulated and studied release behaviour of sustained release ambroxol hydrochloride HPMC matrix tablet. The results of dissolution studies indicated that formulation F-V (drug to polymer 1:1.47), the most successful of the study, exhibited drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio. Applying exponential equation, all the formulation tablets (except F-V) showed diffusion-dominated drug release. The mechanism of drug release from F-V was diffusion coupled with erosion (anomalous).

43. **Nashiru Billa et al**\(^{49}\), were prepared Controlled release matrix tablets of Diclofenac sodium using xanthan gum. They studied processing variables at the laboratory and pilot scale that can affect the hydration rates of xanthan gum matrices containing diclofenac sodium and the rate of drug release. They have concluded that the diclofenac sodium release from the laboratory scale and the pilot scale formulation studies was generally linear. Thermal treatment did not appear to have any effect on the rate of drug release; however, hydration of xanthan gum seemed to be affected by the wetness of the powder mass during granulation. Because drug release from xanthan gum matrices proceeds via hydration of the matrix structure, it is important that wetness be properly controlled to avoid variations in rate of drug release among production batches.