AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

A Modified Release Drug Delivery Device: Multilayered Matrix Tablets

Izhar Ahmed Syed[1*], Yamsani Madhusudan Rao [2].

1. SR College of Pharmacy, Ananthsagar , Hasanparthy Warangal -506371.

2. University College of Pharmaceutical Sciences, Kakatiya University , Warangal

ABSTRACT

A new multi-layer tablet design has recently been proposed for constant drug release: It consists of a drug-free barrier layer on one or both bases of an active core (hydrophilic matrix). This partial coating modulates the core hydration process and reduces the surface area available for drug release. The consequence is an extended release that draws close to a linear release profile. These devices are primarily intended for soluble drugs, while an excessive reduction of the release rate may be obtained with drugs of low solubility. In these devices, time-dependent polymeric barrier is planned to control the release of soluble drugs. Oral Controlled release matrix tablets and layered matrix tablets can be formulated for highly water soluble drugs and sparingly soluble drugs by using polymers in the matrix core and as release retardant layers. This devices delivery the drugs to the colon. This review focuses on the application of the multilayered matrix tablets in the design of controlled released dosage forms employing various types of polymers and layered on the matrices core.

Key words: Matrix core, multilayered matrix tablets, zero order release, release retardant layers

*Corresponding Author Email: syed.izharahmed@gmail.com

Received 11 March 2012, Accepted 26 April 2012

Please cite this article in press as: Syed IA *et al.*, A Modified Release Drug Delivery Device: Multilayered Matrix Tablets. American Journal of PharmTech Research 2012.

INTRODUCTION

The oral route of drug delivery is the most convenient and commonly employed route of delivery due to its ease of administration and flexibility in the design of the dosage form. It is well known that modified release dosage forms may offer many advantages over immediate release formulation of the same drug.[1-3] There are numerous ways to design modified release dosage forms for oral administration.[3-6] The design of modified release drug product is usually anticipated to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience.[6-9]

The concept of constant rate drug delivery via the oral route has been achieved and widely popularized through the development of composite dosage forms such as the osmotically–controlled systems and multi particulate design, the primary concern with these systems from technological point of view is the complexity involved in the manufacturing process.[6-9] The another classical way to design a modified release dosage form is by coating tablets, pellets or capsule with insoluble pH–independent polymers.[10-11] However coating is a time-consuming and expensive process with possible problems related to reproducibility of drug release and dose dumping phenomenon.[12-14] The commonly controlled drug delivery devices has been the matrix type such as tablets and granules, where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period. Hydrophilic polymer based (natural and cellulose derivatives) are becoming more popular in formulating oral controlled release tablets.[15] It is well documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time dependent profile.[16] Primarily the drug present at the surface of the matrix is released quickly, leads to burst effect.[17,18] The basic idea was that the multilayered matrix tablets were formulated by comprising of a matrix core containing the active solute and one, or more barriers (modulating layers) incorporated during the tabletting process, containing model drugs release that will maximize a therapeutic benefit or to reduce side effects caused by conventional controlled release tablets.[19,20]. During dissolution process as shown in Figure 1, the swellable barrier swells and gels, but is not eroded, thus acting as a modulating membrane during the release process. The erodible barrier, instead, is progressively removed by the dissolution medium, exposing in time an increasing extent of the planar surface of the core to interaction with the outer environment and to release the drug. These drug delivery devices, will overcomes the major disadvantage of

non-linear release associated with most diffusion controlled matrix devices.[21] The primary aim was to provide zero order release kinetics over an extended period of time. It has also been exploited to achieve delayed delivery for chronopharamaceutical purposes and time controlled colon targeting. The combination of layers, each with different rates of swelling, gelling and erosion is responsible for the rate of drug release within the body. When kept in dissolution media, as time progresses the core swells and the surface area increases to compensate for the decrease in release of the drug concentration. The objective of this review is to focus on the application of the multilayered matrix tablets in the design of oral controlled released dosage form and the polymers used for this type of delivery devices.

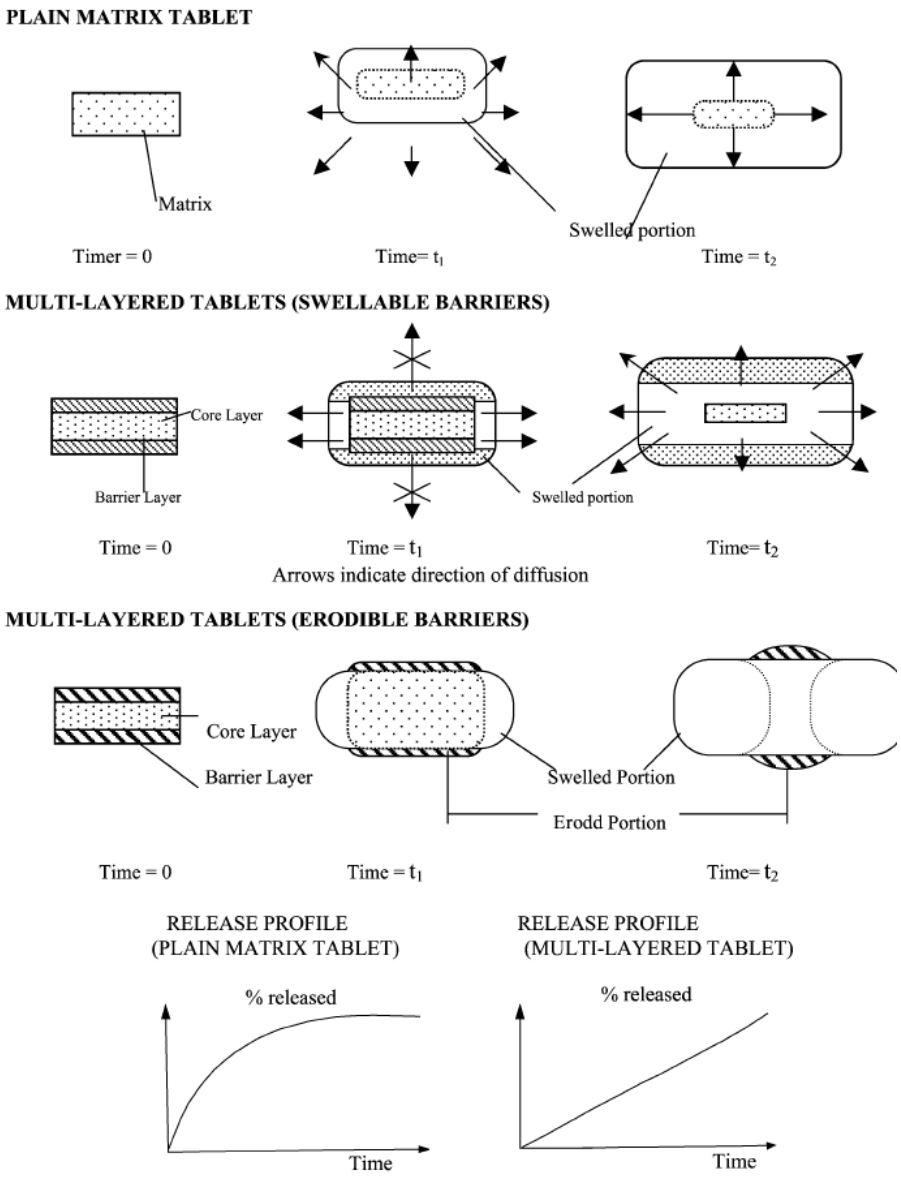

Figure1: Comparison of the release profile of matrix tablets and multilayered matrix tablets.

REASON FOR MULTILAYERED TABLETS

1. Physical/Chemical Separation: It is possible to avoid the incompatibility in between drug –drug and drug-excipients by mean of physical separation. It will be occurred mostly during tablet compression.
2. Immediate Release: Disintegrating monolith deliver the initial quick release required to achieve peak plasma concentration. The addition of initial loading dose in conventional dosage form was neglected by application of such technique.
3. Multiple release profile: Such drug delivery systems are able to provide multiple release kinetics of same or different drugs of same or different physicochemical properties by application of multiple layers. Each monolithic was formulated in order to parcel out the delivery of drug dose by means of different release control mechanisms.
4. Delay Release: Delay release achieved by application of erodible monolithic, which deliver the drug by the second episode of actives in the latter part of gastrointestinal tract.
5. Controlled Release: Swelling monolithic performs by both swelling as well as eroding mechanism in which drug was continuously released throughout the gastrointestinal tract.
6. To produce repeat action: Multilayered tablets readily lend themselves to repeat-action products, where in one layer of the layered tablet or the outer tablet of the compression coated tablet provides the initial dose, rapidly disintegrating in the stomach. The inner tablet is formulated with components that are insoluble in gastric media but release in the intestinal environment
7. Better Management of Release Profile: Layering on the matrix tablet is one of the realistic means of gaining a better management on release profile. It is a viable alternative to conventional matrix tablets to circumvent the initial burst release, and to achieve zero-order release fashion.

MULTILAYERED MATRIX TABLETS

These dosage forms overcome the disadvantages of conventional matrix tablets

Multilayered tablets, for controlled release usually consist of a drug core layer sandwiched by external layers, which may contain dissimilar amounts of drug to form a concentration gradient matrix or just act as a barrier layer.

The drug release modulation from these systems can be accomplished via the following geometric modifications:

(a) Formation of drug concentration gradient and differential erosion of the matrix layers

(b) Restriction of release surface area

(c) The swelling and differential erosion of external layers to maintain constant release.

(d) Differential layer dissolution.

(e) It is applicable for pulsatile or rapid-slow release pattern.

DESIGN OF DEVICES

Generally the drug release mechanism from hydrophilic, swellable matrices is a combination of polymer macromolecular relaxation and drug diffusion. Both the phenomena depend initially on the rate at which water may enter the device.[22]

Multilayered matrix devices are based on the following aspects:

1. Matrix hydration rate and subsequent swelling and/or lowering of diffusion rate.
2. Modulation of the surface of matrix through which the drug can be delivered.

These principles are more effective in the initial phase of the dissolution process and less pronounced as swelling proceeds, leading to linearization of the release profile. To reach similar objective, coating of the matrix tablets selectively on various sides with an inert impermeable film have been attempted. The coating was applied extemporaneously on the tablet faces in order to obtain different coating combinations are represented in Figure 2. Their release performance can be tested by *in vitro* dissolution studies.[23] From the Figure 1 & 2, it may become comprehensible that, as the extent of coating is increased, the release is slowed and the release kinetics approached zero-order. The release rate was mainly determined by the surface geometry of the system as coated–uncoated surface ratio.[24] From these observations it is known that, during dissolution the matrix swells, the coating considerably reduces the drug-releasing surface compared with the uncoated matrix tablets and also implicit towards the ability of coating design to modulate both release extent and kinetics.[25] The casting of impermeable membrane on a portion of the matrix tablet is a manual process. To overcome this drawback, which does not allow for the automatic production of the system, different approaches were tried. In particular, the application of polymeric swellable and erodible barrier layers, as an alternative to impermeable film. The development of the barrier formulation was carried out through two different approaches. The first was based on the use of inert insoluble polymer i.e (ethyl cellulose) and the second was based on the use of hydrophilic swellable polymer (Hydroxy propyl methyl cellulose). The *in-vitro* release performance of such layered tablets and their morphological behavior were examined and compared to that of partial film coated system.[26] The partial film coating does not swell and maintains its original size and shape and offer consistent

release retardation for the whole duration of dissolution process. The barrier made of an inert polymer tends to crack and detach itself from the core within hours after immersion in dissolution media. This effect is due to core volume expansion upon immersion with polymer swelling.[27] This stresses the outer barrier layer, which does not expand to accommodate the swelling of the core. The swellable barriers show a more homogenous system in which both the barrier and the core may swell simultaneously without any internal stress during the dissolution process. The barriers can be applied using a multilayered compression method.[28] The easiest example was represented by either double layer or three layer tablets as shown in Figure 2b and 2c in which only one layer contains the active ingredient, which represents as active core, while one or two other layers act as barrier layers. A substantial time has been devoted to the optimization of suitable barrier formulations that could be applied on the core directly during the compression process.[28] The performance of the final barrier formulation was evaluated using many active cores, compositions proving the efficiency and flexibility of the multilayered devices, particularly in controlling the release of drugs of higher water solubility. Based on this new technique, it extends the release of Diltiazem HCL for more than 24hours[5].

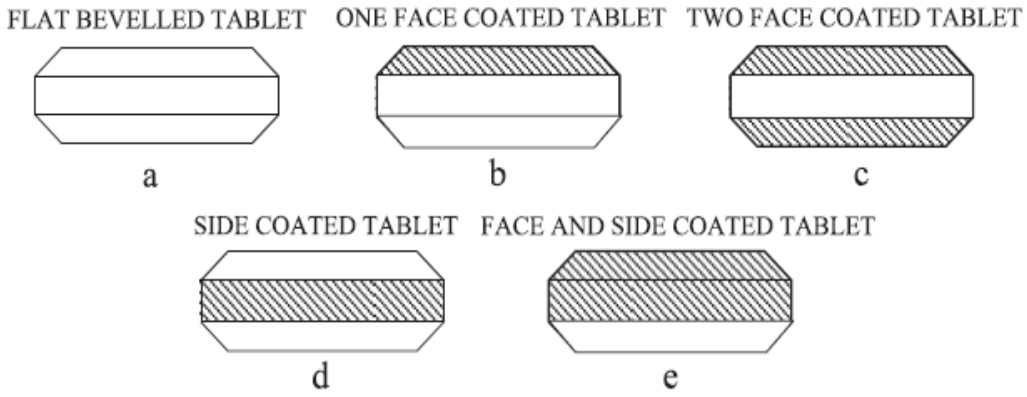

Figure: 2 The diagrammatic representation of a) matrix tablet and other four partially coated designs.

ROLE OF RELEASE RETARDANT LAYERS IN THE MULTILAYERED MATRIX TABLETS

The challenging aspect of controlled drug delivery has been the design of matrix systems that provide zero-order kinetics for total amount of drug release with no lag time or burst effect over a prolonged period and to optimize therapy. Hence the triple layer matrix tablets, with barrier layers between matrix core and dissolution medium.[29] The most common controlled delivery system has been the matrix system containing uniformly dissolved or dispersed drug in the form

of powder or granules, because of its effectiveness as well as low cost and ease of manufacturing. Hydrophilic polymers are becoming very popular in formulating oral controlled release tablets.[30] various synthetic polymers (Ethyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, poly methyl methacrylates etc) and natural polymers (xanthan gum, guar gum, chitosan, carbopol, carrageenan etc.) have been tried by various researchers. It has been shown in Figure 3 that in case of hydrophilic matrices, swelling as well as erosion of the polymer occurs simultaneously and both of them contribute to the overall drug release rate. The movement of the penetrant and polymer fronts and the drug dissolution in highly loaded swellable matrix tablets shows an establishing relationship between front position and drug release kinetics. Three boundaries were identified corresponding to the swelling, diffusion and erosion fronts. The kinetics of drug release depends on the relative movement of the erosion and swelling/diffusion fronts[31, 32]. Under certain conditions of drug solubility and loading in to the matrix core, from reported data it was demonstrated that the difference between the diffusion and erosion fronts is decisive for the release kinetics.[33] The rate of delivery is dependent on the diffusion front velocity. In aspect, when the swelling front accelerated as the porosity increase, it indicates faster dissolution media penetration, but the diffusion front rate remained unchanged, indicating the same amount of drug dissolution rate, the flux remained unmodified.[34] When the solubility of drug was increased and the movement of the erosion front was not significantly affected, both the diffusion front movement and the release rate is increased. It was also interesting to note that the patterns of change of drug release rate were inversely related to the dynamics of gel layer thickness, and the movement of the diffusion front is in linear fashion. The dynamics of gel layer thickness follows the erosion front movement.[35, 36] These consequence is that in swellable matrix tablets the erosion front movement determines the kinetics and the diffusion front, and the rate of drug release. Development of oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist.[29] The reported various application of the barriers layers over the matrix core are summarized in the Table 1.

Advantages Multilayered Matrix Tablets

1. It deliveries the drug for a constant rate.
2. Dose dumping can be avoided.
3. The maximum flexibility in drug release patterns.
4. Ease of manufacturing.
5. Increase in safety margin of high potency drug.

Table 1: Summary of the Multilayered Matrix Tablets

Active Ingredient	Polymer Used in Matrix core	Polymer Used as Barrier Layered	Method of granulation	Reference
Trimetazidine di Hydrochloride	Guar gum	Guar gum	Wet granulation	35
Metoprolol Tartrate	Guar gum	Guar gum	Wet granulation	36
Tramadol HCL	Guar gum	Guar gum	Wet granulation	55
Diltiazem HCL	Xanthan gum and guar gum along with gum ghati	Guar gum	Wet granulation	48
Venlafaxine HCL	Xanthan gum	Xanthan gum	Wet granulation	46,50
Venlafaxine HCL	PEO	PEO	Wet granulation	47
Metoprolol Tartrate	Carragenen, HPMC, Guar gum, xanthan gum Pectin, Chitosan, ethyl cellulose,	Xanthan gum	Direct Compression	49
Isosorbite mononitrate.	Carbopols	Carbopols	Direct Compression	45
Propranolol HCL	Chitin	Ethyl cellulose	Direct Compression	43
Diclofeanc sodium	Guar gum, HPMC	HPC, HPMC, SCMC	Wet granulation	56
Diltiazem HCL	Guar gum	SCMC	Wet granulation	60
Metoprolol tartrate	Xanthan gum	SCMC	Wet granulation	62
Propranolol HCL	chitosan and Xanthan gum	chitosan	Direct Compression	39
Diltiazem HCL	sterculia foetida gum, rice bran wax	sterculia foetida gum	Direct Compression	54
Venlafaxine HCL	HPMC K-100M and Xanthan gum	Xanthan gum	Wet granulation	51
Diltiazem HCL	Xanthan gum sodium alginate.	Xanthan gum	Direct Compression	53
Diclofenac	Guar gum	Guar gum	Wet granulation	65

6. Improved patient convenience.
7. Maximum utilization and reduction in health care cost.
8. Reproducibility and efficacy.
9. Versatility of release control mechanisms.
10. It controlled the release of poorly soluble drugs.
11. Timed release of drugs.
12. Bi-Phasic release of drugs.
13. Release of 2 or more drugs at different rates.

14. Pulsed release of drugs.
15. Safety of use.

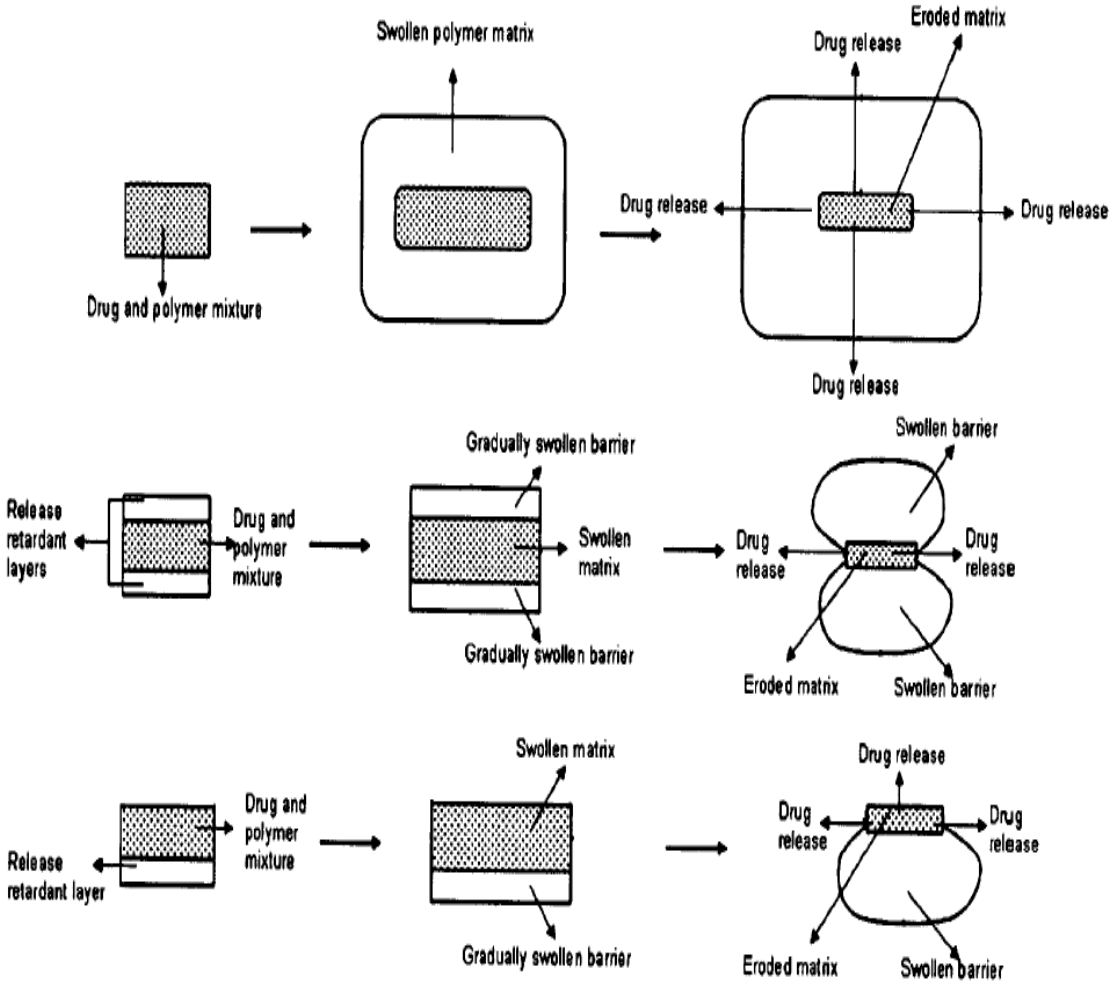

Figure 3: The Effect of barrier layers on the conventional matrix tablets.

The manufacturing of multilayered matrix tablets involves the following steps

The manufacturing of the matrix core tablets is performed in a separate step and is usually done by using a regular rotatory press. Since the barrier layers plays a critical role in the drug release mechanism, its weight, thickness, and compaction need to be tightly controlled during final compression. The process includes the following steps.

1. Dosing of the bottom layer
2. Transfer of the prepared core
3. Insertion into die
4. Dosing of the top layer
5. Final compression
6. Ejection

RECENT APPLICATION OF MULTILAYERED MATRIX TABLETS

Krishnaiah YSR Studied the oral controlled drug delivery systems for highly water soluble drugs using guar gum as a carrier in the form of three-layer matrix tablets of Trimetazidine dihydrochloride (TZH). Matrix tablet granules of guar gum and TZH were prepared by the wet granulation technique using starch paste as a binder. The *in-vitro* drug release studies revealed that the amount of TZH released from the three-layer matrix tablets provided the required release rate on par with the theoretical release rate for guar gum formulations meant for twice daily administration. The results show that guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems of TZH. [35]

Krishnaiah YSR developed and design oral controlled drug delivery systems of metoprolol tartrate (MT) were used along with guar gum as a carrier in the form of a three-layer matrix tablet. Matrix tablets containing guar gum were prepared by wet granulation technique using starch paste as a binder. Matrix tablets of MT were unable to provide the required drug release rate. However, the three-layer guar gum matrix tablets provided the required release rate on par with the theoretical rate of release for MT meant for twice daily administration. The results indicated that guar gum, in the matrix core along with MT for the formulation of three-layer matrix tablets.[36]

Al-Saidan S.M, in his study, pharmacokinetic parameters was evaluated for guar gum-based three layer matrix tablets. The prepared formulations consist of MT& guar gum in the matrix core. The results indicated that plasma concentration of MT showed delayed Tmax; lower Cmax; decreased Ka; unaltered bioavailability and prolonged $t_{1/2}$ indicated a slow and prolonged release of MT from guar gum based three layer matrix tablets in comparison with the immediate release tablet. [44]

Efentakis M. studied sustained release matrix and three-layer tablets based on carbopol with isosorbite mononitrate (ISMN)[45]. Matrix tablets were prepared by direct compression by using Carbopols as carriers, in the form of matrices and three-layer tablets with ISMN. The findings indicated that all systems confirmed sustained release. The properties of the polymer used and the structure of each formulation appear to significantly affect drug release and its release rate. The three layered formulations show lower drug release compared to the plain matrix tablets. It is, due to the fact that the barrier-layers hindered the penetration of liquid into the core and modified drug dissolution and release profile. The geometrical characteristics of the tablets as well as the weight/ thickness of the barriers-layers highly influenced the rate of ISMN. Kinetic

analysis of the data indicated that ISMN release from the plain matrix tablets was mainly attributed to Fickian diffusion, while three layer matrix tablets showed either anomalous diffusion or erosion/relaxation mechanisms. The range of release profiles can easily be obtained through variations in tablet structure for drugs like ISMN.

Thawatchai Phaechamud developed sustainable release of propranolol Hydrochloride (PHCL) tablets using chitin as press–coating material.[38] Tablets coated with chitin and with ethyl cellulose at coating layer of 400mg could prolong the drug release for more than 12hrs. The reelase data were treated with different mathematical model, the results indicated that the release of PHCL from press coated tablets obeyed the first order model.

Gohel M.C, studied venlafaxine hydrochloride–layered tablets for obtaining sustained drug release. The tablets containing venlafaxine hydrochloride were prepared by using xanthan gum (XG) in the middle layer and barrier layers[46]. The drug release rate was found to be dependent on the percentage of XG, pore forming agents like pharmatose DCL -11 and surface area of the layered tablets exposed to the dissolution medium. The results show that sustained drug release was achieved with substantial water uptake and gelling of xanthan gum.

Ahmed A. developed PEO layered tablet formulation and evaluated pharmacokinetics. The *in vivo* study suggests that optimized PEO three-layer formulation developed in this work may be comparable to the marketed Ven HCl capsule in the form coated pellets that are reported to suffer from low productivity, long processing time, and high cost. The pharmacokinetic parameters of VHCl from the optimized three layer tablet were compared to the marketed product (capsule) as a reference in healthy human subjects, using a randomized crossover design. The data obtained revealed the 90% confidence interval for AUC (0-24) and AUC(0-∞) are within (0.8-1.25), which fulfilled the bioequivalence criteria. Hence VHCL extended release extended-release three-layer tablet were formulated for once-daily.[47]

Maulesh G. Studied three layered matrix tablets for zero order release by using xanthan gum and guar gum along with gum ghati; a novel release modifier of diltiazem Hydrochloride. The result concluded that zero order release profile can be successfully achieved by preparing an appropriate blend of guar gum with gum ghati in core and guar in barrier layers. [48]

Esra Baloglu, developed layered matrix tablet of metoprolol tartrate (MT) to reach to the target profile.[49] The different swellable polymers were used in the matrix core and xanthan gum in the barrier layers was used. The result indicates that carrageenan as a hydrophilic polymer in the matrices, to achieve zero order drug release profile of the MT, in the form of layer matrix tablets.

Thawatchai Phaechamud, studied the Propranolol HCl (PHCL) release from the layered tablets containing chitosan and xanthan gum as matrix component were investigated. Increasing the amount of lactose could diminish pH sensitive release behavior of these matrix tablets. The amount of PHCL loading did not affect the PHCL release rate, which was influenced by the hydrodynamic force and the matrix composition. Addition of soluble diluents in core or barrier could increase the PHCL release. Least square fitting the experimental dissolution data to the mathematical expressions (power law, first order, Higuchi's and zero order) was carried out, to study the drug release mechanism.[43] The majority of dissolution profiles of the prepared three-layered tablets provided a better fit to zero order kinetic than to first order kinetic.

Ladani A, developed multilayered matrix (sustained release) tablets of highly water soluble Venlafaxine hydrochloride (VHCL) using natural gums and synthetic polymer (HPMC K-100M and Xanthan gum). The tablets containing VHCL 150 mg were prepared using hybrid wet granulation barrier layer technology, using Xanthan gum and HPMC K 100M as rate controlling ingredient in the middle layer and Xanthan gum in the barrier layers. The radar diagram, similarity factor (f_2) were used to evaluate the similarity of test product with the reference product. The multi layered matrix tablets overcome the problem of nonlinearity associated with diffusion controlled matrix tablets by reducing the surface area of VHCL containing layers exposed to dissolution medium. Drug release kinetic of the optimized triple layered tablets best fits to Higuchi model, where as the release exponent value obtained for Korsmeymer Peppas model. Release mechanism appears to be complex mechanism of swelling, diffusion, erosion and barrier controlled.[51]

Shaikh Rahamathullah, developed controlled release layered matrix tablets of paracetamol and verapamil HCl were developed using hydrophilic and hydrophobic polymers by the wet granulation method. Paracetamol core, two and three layered matrix tablets were formulated using hydrophilic (Metolose 60SH) and hydrophobic (Ethocel 10cP) polymers. The results indicated that hydrophilic layers prolonged the drug release whilst hydrophobic layers had no effect. However, a three layered matrix tablet containing a mixture of Metolose 60SH (20%) and Ethocel 10cP (10%) in the layers had the most sustained duration of drug release with T50% values of 10.97 hours and MDT of 10.50 hours. The drug release from the preparation followed zero order kinetics. Therefore, the paracetamol three layered matrix tablets containing mixture of hydrophilic and hydrophobic polymers had the most sustained drug release[52]. Verapamil HCl core, two and three layered matrix tablets were prepared using several concentrations of hydrophilic polymers. The two and three layered matrix tablets were prepared by varying the

concentrations of polymers in the core and layers whilst keeping the total amount of the polymer in the tablet constant[52]. Formulations containing hydrophilic polymers in the core and layers produced more sustained drug release than formulations containing hydrophobic polymers in the core and layers. *In vivo* study with a two-way crossover design was performed on six rabbits to compare the pharmacokinetic parameters of the hydrophilic three layered matrix tablets and Isoptin® SR as the reference product. There were no differences in Tmax, Cmax and AUC values between the verapamil HCl three layered matrix tablets and Isoptin® SR. Therefore, the verapamil HCl three layered matrix tablets containing the hydrophilic polymer had a similar rate and extent of absorption as Isoptin® SR.[52]

Al-Zoubi N., developed face-centered central composite experimental design was applied in programming the sustained drug release from three-layer matrix tablets. Xanthan gum (XG), sodium alginate (SA) and their 1:1 mixture were employed as the matrix former controlling the release of diltiazem HCl (DH). Cumulative percent release at 2 and 12 h (rel2h, rel12h), shape parameter of the release profiles in Weibull function (b), and exponent in the power law model of Peppas (n), were selected as dependent variables and related to the formulation factors via multiple linear regression analysis using second order polynomial equations including two-factor interaction terms. Simplified equations were derived and response surface analysis enabled the formulation factor effects and interactions to be visualized. It was found that different shapes of release profiles can be obtained corresponding to Weibull shape parameter (b) between 0.311 and 1.247. DH in the intermediate layer or of XG in the outer layers reduced the drug release because of restricted and delayed exposure to the dissolution medium or formation of a stronger diffusion barrier. Highly significant linear correlation ($r = 0.894$, $p < 0.001$) was found between the values of b and the exponent in the power law model of Peppas (n).On the basis of the simplified equations (regression models), and the experimental values of three control formulations confirmed the validity of the suggested models in programming the release behavior by the proposed three-layer tablet system within the experimental domain[53].

Bendgude NT, studied Diltiazem HCL (DH) SR tablets were prepared by direct compression using purified rice bran wax and sterculia foetida gum (SFG) as a matrix former. Three layered matrix tablets containing a highly soluble DH, embedded in hydrophobic rice bran wax matrix middle core and SFG, as hydrophilic barrier layers, press coated to the faces of matrix core to achieve constant rate release. The prolongation of DH release from hydrophobic rice bran wax coated with hydrophilic SFG matrices was achieved. Dissolution study of layered tablet investigate that DH release from both planer surfaces of tablet, lag time for drug release through

barrier layer was apparently longer as the amount of barrier was increased. In this study the DH release mechanism revealed that matrix tablets followed first order kinetics, drug release from cylindrical portion and plane surfaces of tablet were described. Texture analysis (TA) of the hydrophilic polymer supported the way in which the swelling and erosion of SFG gum was done. The TA information is linked with other behaviors including dissolution; swelling and erosion of exposed hydrophilic layer and increase in surface area per unit time were also studied.[54]

FUTURE PERSPECTIVE

Many researchers have made attempts to achieve a zero order or near zero order release, since constant release delivery is the primary goal of controlled release systems. One of these techniques relies on the use of multilayered matrix tablets as drug delivery devices. The barrier layers effective press coating material i.e hydrophilic/hydrophobic polymers on the matrix core controlled the release initially; hence the release can be modulated.[5]

In future, one can expect more number of drugs which required the constant release profile. One of the devices is multilayered matrix tablets; this result is an extended release that draws close to a linear release profile. The device was mainly intended for soluble/sparingly soluble drugs, while an excessive reduction of the release rate may be obtained with drugs of low solubility. A new time-dependent polymeric barrier is to be proposed to control the release of sparingly soluble drugs.[55] Two different barrier compositions (one swellable and one erodible) are applied on active cores containing drugs of different water solubility. (Trapidil, Diclofenac sodium, Ketoprofen, Diltiazem HCL, Metoprolol tartrate, Tramadol HCL and Nicardipine HCL, propranolol HCL).[56-62] During the dissolution, the swellable barrier swells and gels, but is not eroded, thus acting as a modulating membrane during the release process. The erodible barrier is progressively removed by the dissolution medium, exposing in time an increasing extent of the planar surface(s) of the core to interaction with the outer environment and the drug releases. Both types of coatings are able to control drug release from these devices. The swellable barrier shows stronger modulation efficiency and is more suitable to modify the delivery release pattern, the erodible barrier shows a time-dependent coating effect that provides better control of the dissolution profile of sparingly soluble drugs[64]. The *in vivo* transit time for the multilayered matrix tablets also reported that, it crossed the small intestine at 6 hr and retained for longer time in colon at 12hr[60].

CONCLUSION

The key consideration in the design of these devices is the ability to maintain the desired level of the drugs in the blood, the self life and reproducibility. These considerations, attached with the therapeutic benefits of layered matrix drug delivery devices, be supposed to ensure that the current high level of interest in this would extend well in to the future and results in betterment of the patients quality of life. All these studies, could establish the suitability of (natural/ hydrophilic) polymers as matrix forming agents and also as barrier layers modulating the release form the layered matrix core.[63] From industrial point of view these devices can be developed on large scale using layered tablet press. Hence a significant amount of the progress has been achieved in the field of layered matrix tablets that effectively treat disease with continuous release for prolong period. It leads release of the drug to the colon[64].

One of the major benefits of the multilayered matrix tablets is its ability to be easily incorporated into the production line. The multilayered matrix tablets can be manufactured by readily available equipment that can be integrated into widely-used pharmaceutical processes, thus giving firms more control over their own production activities. The marketed product available with this technology is diclofenac–ratio pharm® from skye pharma.

ACKNOWLEDGEMENT

The Principal and Management of SR College of Pharmacy, Warangal for his constant encouragement.

REFERENCES

1. Robinson JR and Vincent HL. Controlled drug delivery system: Fundamentals and Application. Marcel Decker In 1992, 2nd edition 29:180-187.
2. Yie Chien, Novel Drug delivery system. Marcel Decker In 2nd edition 50, pp 3-11, 43-63, 139-177.
3. Banker GS, Anderson NR. In Lachaman L, Lieberman HA and Kanig JL. The Theory and Practice of Industrial Pharmacy, lea and fedbiger, Philadelphia, Bombay, 1986 Ed, pp. 293-345.
4. Pillay V, Fassihi R. A novel approach for constant rate delivery of highly soluble bio actives from a simple monolithic system. J Control Release 2000; 67: 67–78.
5. Shajahan Abdul, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. J. Controlled Release. 2004; 97 (3): 393-405.
6. Conte U, Maggi L, Colombo P, and Manna La A. Multi-layered hydrophilic matrices as constant devices. J. Controlled Release 1993: 26(1): 39-47.

7. Ritschel WA, *et al* .Biopharmaceutics and pharmacokinetic aspects in the design of controlled release per oral drug delivery systems. Drug Dev Ind Pharm 1989; 15: 1073–1103.
8. Maggi L, Bruni R, Conte U. High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms. Int J Pharm 2000; 195:229-238.
9. Conte U, Colombo P, Magi L, La Manna A. Compressed barrier layers for constant drug release in swellable matrix tablets. Proceedings of 6th International Conference on Pharmaceutical Technology. June 2 –4, 1992, Paris, France, 1992; II: 102– 111.
10. Drewe J, Guitard P. *In vitro-in vivo* correlation for modified-release formulations. J. of Pharmaceutical Sciences. 1993; 82 (2): 132-137.
11. Rane M, Parmar J, Rajabi-siahboomi AR. Hydrophilic matrices for oral extended release: Influences of fillers on drug release from HPMC Matrices. Pharma times. 2010; 42, 04:41-45.
12. Conte U, La Manna A, Colombo P, System for the controlled rate release of active substances, U.S. Patent 4,839, 1989; 177: 13.
13. Colombo P, Bettinia R, Santi P, De Ascentiis A, Peppas N.A. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport J. Contr. Release. 1996; 39: 231-237
14. Sadeghi F, Ford JL, Rubinstein MH and Rajabi-Siahboomi AR. Comparative study of drug release from pellets coated with HPMC or Surelease, Drug Dev Ind Pharm 2000; 26 (6): 651–660.
15. Conte U, Maggi L, Colombo P, Manna La A. Multi-layered hydrophilic matrices as constant release devices. J. Control. Rel. 1993; 26: 39-47.
16. Conte U, Colombo P, Maggi L, and Manna La A. Compressed barrier layers for constant drug release in swell able matrix tablets. STP Pharma Sci. 4, 1994; 107-113.
17. Conte U, La Manna A, Colombo P. Tablets with controlled rate release of active substances, U.S. Patent 5,422, 1995;123 06.
18. Colombo P, La Manna A, Conte U. System for the controlled-rate release of active substances. US Patent 4, 1989, 839, 177.
19. Conte U, La Manna A, Colombo P. Tablets with controlled-rate release of active substances. US Patent Application. 1992, 07/926, 380.
20. Qui Yihong, Chidambaram N, Koplette F. Design and Evaluation of layered diffusional matrices for Zero –order sustained release. J. Control. Rel 1998; 51:123-130.

21. Conte U, Maggi L, Torre M. L, Giunchedi P, La Manna A. Press-coated tablets for time-programmed release of drugs. Biomaterials. 1993; 14, 1017-1023.
22. Korsmeyer RW, Gurny R, Doelker E, Bur P, Peppas NA. Mechanisms of solute release from porous hydrophilic. Int. J. Pharm.1983; 15, 25.
23. La Manna A, Conte U, Colombo P. Physical restriction in swellable matrices as modulator of drug release, Eurobiomat Workshop on 'Synthetic Polymer as Drug carriers. Interaction with blood. Pallanza, Italy, 1991; 21– 24.
24. Yang L, Fassihi R. Examination of drug solubility, polymer types, hydrodynamics and loading dose on drug release behavior from a triple-layer asymmetric configuration delivery system. Int J Pharm 1997; 155: 219-229.
25. Conte U, Maggi L. A flexible technology for the linear, pulsatile and delayed release of drugs, allowing for easy accommodation of difficult *in vitro* targets. J Control Release 2000; 64: 263-268.
26. Fassihi R and Ritschel WA. Multiple-layer, direct-compression, controlled-release system: *in vitro* and *in vivo* evaluation. J. Pharm. Sci. 1993; 82: 750-754.
27. Wilding IR, Davis SS, Sparrow AR, Ziemniak JA and Doland LH. Pharamco scintigraphy evaluation of a modified release Geomatrix® Diltiazem formulation. J. Control. Rel**.** 1995; 35: 89-97.
28. Yang L, Venkatesh G, Fassihi R. Compaction simulator study of a novel triple-layer tablet matrix for industrial tabletting. Int J Pharm 1997; 152: 45-52.
29. Frohoff-Hu¨lsmann MA, Schmitz A, Lippold BC. Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxyl propyl methylcellulose as coating material for diffusion pellets: I. Drug release rates from coated pellets. Int J Pharm. 1999; 177:69–82.
30. Langenbucher F, Möller H. Correlation of *in vitro* drug release with *in vivo* response kinetics, Pharm. Ind. 1983; 45 (6): 623–628.
31. Yang L, Fassihi R. Zero-order kinetics from self-correcting floatable asymmetric configuration drug delivery system. J Pharm Sci. 1996; 85: 170 173.
32. Conte U, Maggi L. Modulation of dissolution profiles from Geomatrix® multi-layer matrix tablets containing drugs of different solubility. Biomaterials. 1996, 17(9): 889-896.
33. Conte U, Maggi L, Giunchedi P, Sangalli ME, La Manna A. Multi layer hydrophilic matrix tablets as controlled delivery system. Proceedings of the II European symposium

on Controlled Drug Delivery. April 1-3,1992Noordwijk Aan Zee, the Netherlands, 1992; 117-120.

34. Streubel A, Siepmann J, Peppas NA, Bodmeier R. Bimodal drug release achieved with multi-layer matrix tablets: transport mechanism and device design. J Control Rel**ease** 2000;69: 455-468.
35. Krishnaiah YSR, Karthikeyan RS, Gouri Sankar V, Satyanarayana V. Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride. J Controlled Release 2002;81:45–56
36. Krishnaiah YS, karthikeyan RS, Satyanarayana V. A three layer guar gum matrix tablets formulation for oral controlled delivery of highly soluble metoprolol tartrate. Int J Pharm. 2002; 24: 353-366.
37. Libo Yang, Reza Fassihi. Modulation of diclofenac sodium release from totally soluble controlled release drug delivery system. J Control Rel 1997; 44: 135-140.
38. Thawatchi P, Garnpimol CR. Controlled Release of Propranolol HCl from chitosan-Lactose-Xanthan gum Matrix Tablets. Poster Pres, Thai Conference.04.:411-413
39. Thawatchi P. Effect of particle size of chitosan on drug release from layered matrix system comprising chitosan and Xanthan gum Pharmaceutical and Health Science J 2008; (3) 1: 1-11.
40. Thawatchi P. Comparison Drug Release from Simple and Layered Matrix Systems Containing Hydroxypropyl Methylcellulose. Thai Pharmaceutical and Health Science J 2008; (3) 2:219-228.
41. Thawatchi P. Variables Influencing drug release from layered Matrix system Comprising Hydroxypropyl Methyl Cellulose. AAPS Pharm Sci Tech 2008; 92: 668-674.
42. Thawatchi P, Garnpimol CR. Formulation variables influencing drug release from layered Matrix system Comprising Chitosan and Xanthan gum. AAPS Pharm Sci Tech. 2008; 9(3): 870-877.
43. Thawatchi P *et al* Sustainable Release of Propranolol Hydrochloride Tablets using Chitin as Press-Coating Material.148-159.
44. Al-saidan SM, Krishnaiah YSR, Satyanaryana V, Bhaskar P, Karthikeyan RS. Pharmacokinetics evaluation of guar gum based three layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug. Eur J. Pharm 2004; 58: 697-703.

45. Efentakis M, Peponaki C. Formulation study and Evaluation of Matrix and three- layer Tablets sustained Drug Delivery Systems Based on Carbopol with Isosorbite Mononitrate. AAPS Pharm Sci Tech. 2008; 9(3): 917-923.
46. Gohel MC, Bariya SH. Fabrication of triple –layer Matrix tablets of venlafaxine hydrochloride using xanthan gum. AAPS Pharm Sci Tech. 2009; 10(2): 624-630.
47. Ahmed A, Aboel wafa, Emad B. Basalious Optimization and In vivo Pharmacokinetic Study of a Novel Controlled Release Venlafaxine Hydrochloride Three-Layer Tablet AAPS PharmSciTech; 2010;11 (3): 563-572.
48. Maulesh G. Joshi, Setty CM, Deshmukh AS, Bhatt YA. Gum Ghati: A New release modifier for zero order Release in 3–layered Tablets of Diltiazem Hydrochloride. Indian J Edu Res 2010; 44(1): 78-85
49. Esra B, Taner S. A Design and Evaluation of Layered Matrix Tablet Formulations of Metoprolol Tartrate. AAPS Pharm Sci Tech. 2010; 11(2): 563-572
50. Gohel MC, Soni CD, Nagori SA and Sarvaiya KG. Modulation of venlafaxine hydrochloride release from Press coated matrix tablets Indian J.P. Sci.2008 ;(2): 292-296.
51. Ladani A, Patel M, Patel V. Fabrication of multi-layer matrix tablets of venlafaxine hydrochloride using hypromellose and xanthan gum. Int J Drug Develop Res 201; 3 (3): 291-299
52. Shaikh Rahamathullah. Design and Evaluation of Controlled Release Layered Matrix Tablets of Paracetamol and Verapamil HCL
53. Al-Zoubi1 N, Malamataris S. Three-layer matrix tablets and simple approach of drug release programming. J Drug Del Sci Tech 2008; 18 (6):431-437.
54. BendgudeNT, Vidya RI, Sushilkumar, S. Poddar. Sustained release from Layered Matrix System Comprising Rice Bran Wax and Sterculia Foetida Gum. Int J Pharm Tech Res 2010; 2 (1):989-1005.
55. Ravi S, Reshu G, Deepa P, Kamal P. Preparation and Evaluation of three layer matrix tablets for Oral Controlled Delivery of Tramadol HCL. Pharma Bio World, 2007; 1: 59-64.
56. Syed IA, sunil R**,** Sri SP, Kalamata VN and Yamsani MR. Modulating the Release of Diclofenac Sodium Matrix cores Layered with Hydroxypropyl Cellulose, Hydroxypropyl Methyl Celluose and Sodium Carboxy Methyl Cellulose. Indian Drugs. 2009; 46(4): 304-309.

57. Ahmed SI**,** Mohan SJ, Rao YM. Modulating the release behavior and kinetic Evaluation of diclofenac sodium from natural polymers. Int J Chem Tech Res 2010; 2(2):834-841.
58. Ahmed SI, Lakshmi NM, Rao YM. Formulation and Characterization of Matrix and Triple-layer Matrix Tablets for Oral Controlled Drug Delivery Systems, Int J Pharm Pharma Sci 2010; 2(3): 137-143.
59. Ahmed SI**,** Narsu ML, Mohan SJ, Rao YM. Formulation Study and Evaluation of Matrix and Three-Layer Matrix Tablets Oral Controlled Drug Delivery System Based on Xanthan Gum and Locust Bean Gum, Int J Pharma Sci Nanotech. 2010; 3(2): 1012-1020.
60. Ahmed SI, Lakshmi NM, Rao YM. Formulation and Evaluation of Multilayered matrix tablets of Diltiazem hydrochloride. Lat. Am J Pharm 2011; 30 (4): 721-8
61. Ahmed SI, Lakshmi NM, Rao YM. Formulation Characterization and Optimization of Layered Matrix Tablets for Controlled Delivery of Diltiazem HCl J Pharma Res 2010; 3(12): 2863-2867.
62. Ahmed SI, Lakshmi NM, Rao YM. Formulation and Characterization of Matrix and Triple-Layer matrix tablets for Controlled Delivery of Metoprolol Tartrate, Int J Pharm Sci Drug Res 2011; 3(1): 23-28
63. Ahmed SI, Lakshmi NM and Rao YM. In *vitro* Release kinetics and Bio availability of Layered Matrix tablets of Diclofenac Sodium. Int J. Drug Deli 2011; 3:286-292
64. Ahmed SI, Lakshmi NM and Rao YM. In *vitro* Release kinetics and Bio availability of Layered Matrix tablets of Diltiazem Hydrochloride. Int J Drug Dev Res 2011; 3 (1): 234-241.
65. Chavda HV, Patel MS and Patel CN Preparation and *in vitro* evaluation of guar gum based triple-layer matrix tablet of diclofenac sodium. Res Pharm Sci 2012; 7(1): 57-64