2.0 LITERATURE REVIEW

2.1 DIABETES MELLITUS & ITS TREATMENT

T2DM (type 2 diabetes mellitus) is a progressive and complex disorder for which long term treatment is required. Majorly for obese patients, with progressive loss of islet beta-cell function, monotherapy is not sufficient and require insulin therapy alone or in conjunction with oral antidiabetic therapeutic agents to maintain proper glycaemic control (Krentz & Bailey 2005). Pelikánova, 2009) defines hyperglycemia as feature and self-governing diagnostic criteria of metabolic syndrome (MeTS).

The first incident of diabetes was documented 3500 years ago by the Ancient Egyptians. Aretaeus, practiced in Cappadocia around 120 AD, gave the first clinical descriptions about diabetes (King et al., 1999). Since 1945, The incidence of diabetes has been folded in every 20 years (Barnett, 1998). 171 million in 2000, (Wild et al., 2000); 285 million, in 2010(Shaw et al., 2010); 382 million 2013 (Guariguata et al., 2014), and will reach 439 million adults by 2030 (Shaw et al., 2010) and 592 million by 2035 (Guariguata et al., 2014).

In newly diagnosed patients with T2DM, welfares of microvascular complications and increased glycaemic control were established by the UKPDS (United Kingdom Prospective Diabetes Study). However, it was unrevealed for macrovascular disease, with neither sulphonylureas nor insulin significantly reducing cardiovascular events (Krentz & Bailey 2005). Further the diabetic patient are at higher risk of cerebrovascular diseases and concentration must be focused on cardiovascular risk factors to treat both together and patients with the low CV risk should have HbA1c level below 4.5%. In such cases both diseade should be treated individually and one has to change his/her life style as soon as diabetes diagnosed positive (Pelikánova, 2009).

In the UKPDS, overweight and obese patients randomized to initial metformin monotherapy the results showed drop in myocardial infarction and diabetes-related deaths significantly (Krentz & Bailey 2005). In hyperglycemia, metformin is the medicine of choice and if monotherapy does not supply acceptable control over sugar,
other oral antidiabetics or insulin should be supply in the combination (Pelikánova, 2009). Hundal et al.,2000 examine the mechanism of metformin for reducing glucose level in T2DM patients. In their clinical study authors observed that the glucose production rate was twofold reduced in control subjects compared to the diabetic subjects and after metformin treatment, gluconeogenesis reduced by 33% in diabetic subjects. Based on absence of glycogen cycling in the control subjects, compared to 25% of glucose production by glycogen cycling, it was concluded that Metformin lowered the rate of glucose production in these patients through a reduction in gluconeogenesis. WHO, World health organization, 2013) updates a list of essential medicines every two years since 1977. This model List includes minimum medicine required for a basic health-care arrangements, listing the most efficacious, safe and cost-effective medicines for disease in priority conditions. In latest 16th edition of World Health Organization Model List of Essential Medicines, Metformin is one of only two oral antidiabetics. Gonzalez-Angulo & Meric-Bernstam, 2010 carried out a detail study on metformin. They observed metformin having excellent glycemic control by dropping circulating glucose and enhancing insulin sensitivity. They also observed metformin having antineoplastic effects in all breast cancer subtypes as well as in cytotoxic therapy-resistant models in their study as well as in available data.

Repaglinide defined as a very first carbamoylmethyl benzoic acid derivative class of oral antidiabetic agents intended to control postprandial glucose in patients with T2DM (Culy & Jarvis, 2001). Like the sulphonylureas, repaglinide achieves glycemic control by increase insulin secretion by β cells of pancreas, but differs in its binding mechanism, extent of action and excretion mode. Double-blind, randomized clinical trials were carried out for 1 yr time period and the result showed that repaglinide gives similar control than sulphonylurea with reduction in risk of hypoglycaemia. The most importantly additive glycemic control observed when combination therapy of repaglinide with metformin was given with good tolerance even in disturbance in number & time of meal (Culy & Jarvis, 2001). Gomis, 1999 studied action of repaglinide to establish the effective dose range in two placebo-controlled studies. One of the studies showed dose-dependent reduction in blood glucose reverse condition raise in insulin. Repaglinide decreased FPG 3.4 mmol/L and postprandial 5.8 mmol/L in comparision to placebo. In other double-blind, study,
repaglinide with dose 0.5-4.0 mg was compared with the sulphonylureas. The result proved repaglinide superior to glipizide and was similar to glibenclamide and gliclazide in HbA1c reduction. Repaglinide proved to be effective in patients with T2DM as monotherapy. Stein et al., 2012 point out on several new agents in treatment of diabetes and carry out a review on these agents. In case of metformin serious hypoglycemia or weight gain, in case of sulfonylureas, frequent dosing or expense in case of meglitinide, use of conventional agents become limited and other anti diabetic agents are required. Repaglinide is a meglitinide analog and due to its short duration of action its control release will reduce dosing frequency, amount of drug and thereby cost. Very important hypothesis by Shigeto et al., 2007 that the additional mechanisms of insulin secretion enhanced by glinides, to prove the hypothesis they examined the pattern of instance of insulin secretion in presence of different agents. The results of the study showed that glinides enhanced insulin secretion even in Ca2+-depleted medium and it was concluded that glinides having two pathways mechanism, dependent and independent pathway through K(ATP) channels.

**Combination Therapy for Diabetes**

Monotherapies in chronic and progressive T2DM is not sufficient for glycemic control and thus co-administration of oral antidiabetic drugs are being prescribed since last few years. It is difficult for patient to manage two or more drugs at a time so use of single table with two therapeutic agents enhances patient compliance and may enhance intensity of therapy. Insulin sensitizer and an insulin secretagogue have a rational oral antidiabetic combination, as dual endocrine defects of insulin resistance and impaired beta-cell function in T2DM (Howlett et al., 2003). A study on ‘whether outcomes to safety and efficacy with oral antidiabetic agents when used as FDC-fixed dose combination or LPC- loose-pill combination therapies are same or not for patients with T2DM’ was carried out by Hutchins et al., 2011. The outcome suggested that T2DM patients treated with FDCT may have better therapy, improved compliance, and lower costs, in contrast to those treated with LPCT (Hutchins et al., 2011). Monotherapy is a first line pharmacologic treatment option. However, with oral antidiabetic agent to maintain glycemic control, extra oral antidiabetic agents are often taken as a dual therapy (Sakane, 2012). In dual therapy separate pills or a single pill containing two drugs are prescribed. In further studies were carried out by
Sakane, 2012 on randomized controlled patients requiring dual therapy and the results showed that FDCT gave more efficacy contrast to LPCT. As a part of result he concluded that T2DM patients with FDCT may have better adherence, improved satisfaction, and lower direct costs, compared to those treated with loose-pill combination therapies (Sakane, 2012).

Bailey & Day, 2009 explains that in management of T2DM, with other antidiabetics, metformin is often combined to have different mechanism of action. Two single tablets are in inconvenient for patient and now fixed dose mono tablet available with 2 therapeutic agents. They also state that fixed-dose combination therapies (FDCT) offer ease, reduce the pill load and ease dosage regimens, better glycaemic control for the patient compared to loose-pill combination therapies (LPCT). Currently metformin is prescribed with combination of all other class of antidiabetic class drug (Bailey & Day, 2009). Study carried out by Plosker and Figgitt, 2004 showed that repaglinide in combination therapy with metformin or rosiglitazone gives better effect than the metformin or rosiglitazone alone. Further repaglinide showed similar glycaemic control as glibenclamide give. The review also point out on a Canadian study that showed a positive cost-effectiveness ratio for patients who change therapy from a sulphonylurea to repaglinide versus those who remained on sulphonylurea therapy. It was observed that hypoglycaemic episodes compared to some sulphonylureas are less common with repaglinide (Plosker and Figgitt 2004).
2.2 FORMULATION STUDIES

2.2.1 METFORMIN HYDROCHLORIDE

Kumar, 2000 gave detail description about Metformin and described that Metformin HCl is hygroscopic in nature and not directly compressible and thus formulation steps increases that may include wet granulation or dry granulation or other. In this research work various excipients can enhance the flow and compression properties of the drug. Aerosil provide optimal flow so that consistent die fill and weight control can be achieved. HPMC and HPC as binder used that provide metformin HCl sufficient cohesive properties and DBC anhydrous and MCC allows to be compressed using the direct compression technique. MCC in addition gives anti adherence virtue. With the help of this excipients and other basic material direct compressible metformin HCl tablets were prepared and patent grant was achieved in year 2000.

Chandira et al., 2010 carried out study on antihyperglycemic, Metformin Hcl for T2-NIDDM. The ER formulation was prepared for, prolongs drug absorption in the upper-GI tract that permits once daily and may enhance patient compliance with oral therapy compared Conventional form. It was observed that Metformin HCl presented problem due to its poor direct compressibility, high water solubility and high dose. Extended release matrix tablets were formulated and evaluated including drug release stability studied as per ICH guidelines.

Senthil et al., 2013 state that hygroscopicity and aqueous solubility more than 300 mg/ml at 25°C of metformin HCl presents formulation and stability issue, so the study was carried out to make a free-flowing and cohesive metformin HCl that becomes directly compressible. In this study dual approach was employed, recrystallization of API as well as use of directly compressible excipients. Anti-solvent method was applied to re-crystallize metformin HCl using PVP K30 in different concentration and time. Processing conditions were optimized using $3^2$ factorial design.

Mandal et al., 2007 aimed to design an oral SR matrix tablet of metformin HCl and its optimization. As matformin is hydrophilic drug and it absorbs from GIT
slowly and incompletely thus bioavailability 50-60% (500 mg dose). Its elimination \( t_{1/2} \) is 1.5 to 4.5. Side-effects and 2-3 times dosing per day reduce patient compliance and thus requirement of sustain release of Metformin arises. The authors achieve their goal using HPMC K 15M as matrixing polymer using non-aqueous wet granulation technique.

Jain and Gupta, 2009 used Gelucire and formulated metformin hydrochloride(MH) Floating DDS. The beads were formulated and evaluated for surface morphology, particle size, percent yield, percent drug entrapment, in vitro floating ability, DSC and in vitro drug release. The obtained beads were hard enough and in size range of 3.85 to 3.95 mm with spherical shape. Good floating characteristics were observed and DSC study revealed no significant interaction between lipid and metformin HCl. Good controlled release property was obtained up to 8 h floating time but HSM photomicrograph revealed some non-melted portion at normal body temperature. The reason behind non melted portion was because of Gelucire melting initiate at 47° C and complete melt on 51° C, this property may hinder release profile and batch to batch variation obtained as drug may remain intact in non-melted beads.

Nayak et al., 2011 aimed to develop floating beads of metformin hydrochloride using alginate for treatment of T2DM. Evaluations of beads were carried out including 45 days Stability studies. The in vitro release mechanism follows non-Fickian diffusion. In vivo studies showed good blood glucose control and improved the patient compliance by enhancing, controlling and extending the systemic absorption of metformin hydrochloride.

Jabbour and Ziring, 2011 explain merits of XR matformin in T2DM patients. They describe that although XR-matformin is more expensive than immediate-release Metformin; it improves GI tolerability and allows once-daily dosing. Both the dosage gives same exposure at a given total daily dose and gives same effect but XR-matformin shows better patient adherence that may result in greater glycemic control which in turn improve results and reduce health care usage and expenses.
2.2.2 REPAGLINIDE

Malaisse, 2003, In 1995, meglitinide analogs such as repaglinide, nateglinide, and mitiglinide were made known to cover new molecules proposed as non-sulfonylurea. Several experiments on rat were carried out to check potency of repaglinide and mitiglinide. Repaglinide showed rapid increase in plasma insulin than glibenclamide or glimepiride. Onset of nateglinide effect is further quicker and extent of effect shorter compare to glibenclamide. The meglitinides present the advantage over the sulfonylurea glibenclamide of minimizing the risk of undesirable hypoglycemia.

Kavitha & Sathali, 2012 carried out repaglinide solubility enhancement using solid dispersion (SD) procedure. Repaginide a BCS class II, having low aqua-solubility and bioavailability so SD techniques were employed to enhance its aqueous solubility. Using different carrier and in different ratios, 24 set were prepared and evaluated. The results showed that solvent evaporation process having faster drug release than any other technique. Among different careers, PVP K-30 showed better release characteristics.

Jain et al., 2005 prepared controlled release repaglinide formulation that increase stomach residence time without contacting mucosa through the emulsion solvent diffusion processed microspheres. In the study calcium silicate (FLR) as porous carrier with eudragit-s as polymer were used and formulation obtained was pours and even shaped. The floating behavior and clinical study proves that the system formulated with repaglinide can be promising system to improve bioavailability as it was 3.17 times more than marketed formulation.

Jain et al., 2007 in another study repaglinide granule prepared using porous calcium silicate as carrier and HPMC K4M, carbopol 940 and EC as matrix forming polymers and evaluated. The in vivo release study in comparison with marketed formulation revealed increase in repaglinide bioavailability 3.8 fold.

Harika et al., 2013 carried out study on repaglinide with cyclodextrin complexation for sustained release formulation. The complexation was carried out in 1:1 molar ratio and it was characterized by FTIR study. The bio-adhesive sustained
release tablet was prepared using HPMC, Sodium CMC and Carbopol for buccal delivery. The ex-vivo permeation studies revealed that the SR tablets containing repaglinide–HP-β-CD solid complex significantly increase permeation compared conventional formulation, which could be attributed to both, the existence of the drug-CD complex formation and the polymers. It was concluded that formulations with inclusion complexes can be successfully used for SR buccal delivery that improved drug release and permeability.

Deshmukh & Shaikh, 2012 carried out study on solubility improvement of repaglinide by complexation ultimately for improvement in bioavailability. In the study the influence of pH and co-solvent, ethanol on solubilization of repaglinide by HP β-CD were also studied. The complexes were prepared with β-CD and HP β-CD with 1:1 Molar ratio. The results showed markedly enhanced solubility in basic pH and by addition of co-solvent ethanol also.

2.2.3 IN COMBINATION

Hoelscher et al., 2008 carried out studies to determine (1) the bioequivalence of a FDC of repaglinide/metformin 2 mg/500 mg versus co-administration of separate formulations with same dose as and (2) a contrast of the dose proportionality of repaglinide/metformin FDC tablet having 1 mg/500 mg and 2 mg/500 mg dose. The outcome of the studies showed that repaglinide/metformin 2 mg/500 mg and co-administration of separate formulations with same dose were found bioequivalent. Further dose proportionality of repaglinide/metformin FDC tablet showed no unexpected safety concerns were noted and recommend that FDC tablets of repaglinide and metformin with safety and efficacy similar to that of repaglinide and metformin administered as individual formulations.

Hojgaard et al., 2009 in their patent art comprising repaglinide in mixture with metformin or a salt thereof in a dosage form wherein a spray drying of the repaglinide was carried out to make it pH independent and improved dissolution profile with a relative humidity of less than about 25 % before mixing with the metformin or a salt thereof. The formulation developed was immediate release formulation pattern and required to take more than one time a day.
2.3 ORAL CONTROLLED RELEASE SYSTEMS

In formulation of controlled release systems, ODDS (oral drug delivery systems) are the most convenient formulations.

The ODDS have been the most current effectively and widely accepted by large numbers of patients due to its conveniences easy consumption and flexibility to design novelty in them for formulator. It also provides reproducible & easy production with least manufacture cost.

The ODDS have gained attention as newer techniques and advancements by its fabrication are possible that makes possible to achieve desire release rates for formulations. Dissolution, diffusion or both in combination are the common mechanisms that produce desire release in gastro-intestinal milieu.

The systems while preparation of SR formulation, need to focus on properties of drug i.e. dose, ADME rate, its physico-chemical behavior etc. With the use of these properties one can approximate a release rate. These formulation systems have been successfully used to once a day to once a week dosing frequency, for improved patient suitability and compliance, reduction in GI side effects and toxic effects, controlling plasma drug peak & troughs and improved stability of the drug.

The majority types of oral formulations for controlled release systems are

I. Matrix tablets

Matrix tablets are monolithic systems where drug is consistently spread all over a rate controlling medium. Hydrophobic and hydrophilic matrices are the currently used in this system. For BCS class I and class III drugs; the hydrophobic or mixture of hydrophobic and hydrophilic matrices are mixed. For class II drugs, hydrophilic matrices are preferred usually. The dissolution rate of drug is controlled by regulating the rate of diffusion of dissolution fluid in to the matrix or its wettability and thereafter either by pore formation, channels formation, erosion or combination of those mechanisms. The numbers of polymeric materials for such preparation are, HCO, bees wax, xanthum gum, HPMC, and ethyl cellulose and many more.
II. Mucoadhesive tablets

Mucoadhesive oral formulations are the type controlled release formulations that bind to the epithelial surface of stomach or mucin and give SR for longer period of time over there. Role of mucoadhesive polymers are important in retaining formulation by adhesion to biological or mucosal surface. The polymers used are water insoluble and/or water soluble that may be swelling or the cross linking agents. Numbers of polymers for such preparation are sodium carboxymethylcellulose (Na-CMC), carbopol, sodium alginate, HPMC, polycarbophil and gelatin. Such formulations can be formulated in tablets, patches, films and solutions dosage form for oral, buccal, vaginal, rectal and ocular routes.

In research study, two-layer buccoadhesive tablets of acitretin was prepared to achieve a wide range of release rate, HPMC with altered viscosity grades were used. A good relation of IVIVC was obtained by Minghetti et al., 1998. In different study, buccoadhesive erodible tablets of clotrimazole (CLT) for the oral cavity were developed using different bioadhesive polymers. The total adhesion & drug release were found to depend on type of polymer (Khanna et al., 1996).

III. Microcapsules and microspheres

The polymeric particles ranging in size from 1-1000 µm have also drawn much attention in preparation of control release formulations. Various methods for formulation such as interfacial-polymerization, coacervation-phase separation, Sol-evaporation are used to prepare microcapsules/microspheres. The depth of the coat that is responsible for desire release rate can be very as per amount of polymeric material used. Wide variety of natural and/or synthetic polymers depending on the API to be coated and the release characteristics needed can be used.

IV. Floating tablets

Gastric retention by floating are intended for the drug release in upper GI region that may be for local action or for systemic action. These formulations are designed in such a way that system reduces its density than GI fluid. The floating of
formulation is achieved by reduction in density that may be either pores formation or swelling mechanism.

In these approach by density alteration the formulation is meant to be in stomach for desire time-period, where it continuously release drug. The SR formulation preparation was achieved by floating, swellable, and bioadhesive polymer properties. In the study various release hindering polymers like husk psyllium, HPMCK15M, and a swelling agent crosspovidone in various amount were tried and optimized to get the release profile for 12 hours with floating properties due to altered density (Belgamwar et al., 2009). A SR floating capsules reduce it density <1 when comes in contact with stomach media and remained floating in the fluid. The prepared formulation containing chordiazepoxide gave sustain release up to 7 h (Rajak et al., 2011)

V. Osmotic tablets

The essential parts of osmotic formulations are rigid, semi permeable membrane which approx. 300 µm aperture and osmogens. The liquid media enter to the formulation through aperture, the osmogens will create osmotic pressure and the content present in membrane will come out as a part of pressure relief.

The osmotic drug delivery are concentration dependent systems that gives controlled drug release at almost zero order (Malaterre et al., 2009). Thombre et al., 2004 developed SCT (swellable-core technology). The SCT were formulated using drug (core) and polymers that can swells, which create osmotic pressure to deliver drug. Various drugs were tried to check consistency of formulation. Further the pharmacokinetic studies were carried out that establish positive correlation between invitro & invivo drug release. Shokri et al. 2008 developed innovative EOP tablet (elementary osmotic pump). The systematic drug release from orifice by swellable polymer was observed by EOP. Zero order controlled drug release was obtained for about 24 h from the formulation. In another study, naproxen –Na OP tablets evaluated after preparation. The study mainly focused on caring out zero order kinetic rate & to achieve that focus were given on outer membrane formation (Ramakrishna et al., 2002). Waterman et al., (2009) developed a new controlled-release; extrudable core system tablet which osmotically delivers very high doses medicament of low
solubility medicament. The core was formed in an oval shape with a coating semi-permeable in nature. The formulation had shown successfully control delivery of API with high drug loading efficiency. Dong Li et al., (2004) developed a EOPT of Traditional Chinese Medicine Compound Recipe for water insoluble drugs that can be designed to EOP tablet for more complete and sustain dissolution release. Zentner et al in 1985 considered the zero-order medicament release of osmotically active, water soluble agents from tablets coated with controlled porosity walls. The osmotically actuated concept of drug delivery on an equivalent mass per unit surface area basis was tried for SR dosage form. An innovative pulsed-release system based on bilayer coated tablets containing an osmotically active agent that give both diffusion and osmotic pumping effect in drug release using various excipients (Zhang et al., 2003)

Micro and multiple emulsions, Ion-exchange resins Film coated tablets, Electrically stimulated release devices are also controlled release formulations
2.4 FORMULATION TECHNIQUES

Matrix tablets for controlling API release is the simplest approach among all other SR-CR formulations. Role of polymer is very important in this formulations.

I. Direct compression

The term direct compression refers the manufacturing process, in which the tablets are compressed or compacted directly from powder blends of drug and excipients without further manipulation (Wells et al., 2002; Ansel et al., 2005; Augsburger, et al., 2002; Gohel, 2005). In wet granulation method there is granulation before compression, while in DC no granulation is required. It is easier than wet granulation as fewer unit operations are used (Wells et al., 2002; Ansel et al., 2005; Augsburger, et al., 2002; Gohel, 2005). However, to avoid the formulation failure of this method due to its simplicity some critical aspects, such as compressibility and flowability the materials are seriously considered. As this method has some advantages and disadvantages which are listed in the table 1.1 (Wells et al., 2002; Ansel et al., 2005; Augsburger, et al., 2002; Gohel, 2005).

Table 2.1 Merits & demerits for direct compression method

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Fewer unit operations</td>
<td>1  Particles segregations</td>
</tr>
<tr>
<td>2  Anhydrous process</td>
<td>2  APIs contents may be limited</td>
</tr>
<tr>
<td>3  No drying procedures</td>
<td>3  Unsuitable for poor flowing APIs</td>
</tr>
<tr>
<td>4  Faster dissolution rates achieved</td>
<td>4  Static charges on drug may lead to poor flow</td>
</tr>
<tr>
<td>5  Fewer excipients may be required</td>
<td>5  Not applicable to low bulk density materials</td>
</tr>
<tr>
<td>6  Economical</td>
<td></td>
</tr>
</tbody>
</table>
II. Dry granulation technique

The dry granulation involves aggregation of powder by compaction (Wells et al., 2002) either by roller compaction or slug formulation by large tablet formation. No liquid used for granules preparation and mechanical force required. Many disadvantages of dry granulation are capping, lamination and high friability.

Shalini, 2012, carried out a vast study on different types of excipients that may enhance bioavailability and concluded that type amount and interaction with API are responsible for bioavailability. The thorough study of excipients along with their physical, chemical properties of the safety, precautions to handle them also required for intended formulation. In the study how dry granulation affects formulation process variables was determined. Thoorens et al., 2014, formulated tablets by dry granulation and by direct compression (DC) using MCC. DC remains the most cost effective technique for oral solid dosage and dry binding properties of MCC has best use of it.

Table 2.2 Merits & demerits for dry granulation method

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Less equipments</td>
<td>1. No Uniform color</td>
</tr>
<tr>
<td>2. Elimination of Binders</td>
<td>2. Produce large amount of dust</td>
</tr>
<tr>
<td></td>
<td>3. Capping, Lamination are more frequent</td>
</tr>
</tbody>
</table>

Gattu et al., 2012 aimed to formulate, which contains a FDC of clopidogrel and acetylsalicylic acid as film-coated immediate-release tablet formulations. The formulation was prepared by dry granulation and intended for added suitability to the patients by restricting the no. of tablets taken by them.
Dahl et al., 2014 formulate a composition by dry granulation including Tenofovir DF and Emtricitabine, and its methods. Dry granulation unpredictably create its importance in formulating tenofovir DF comprising emtricitabine and efavirenz.

III. Wet granulation technique

Wet granulation is a method of tablets preparation, in which APIs are mixed with excipients and appropriate binding solution to form agglomerate. From this agglomerate larger, multi-particulate entities called granules are formed (Wells et al., 2002; Augsburger et al., 2002; Wauters et al., 2002; Lister et al., 2001; Iverson et al., 2001; Badway et al., 2000). In manufacturing of tablets by wet granulation method, granulation is often an important step as segregation of the components of the powder may be prevented or minimized by the formation of granules. These granules also provide better flow properties to powder blend (Wells et al., 2002; Augsburger et al., 2002; Wauters et al., 2002; Lister et al., 2001; Iverson et al., 2001; Badway et al., 2000). As compared to the individual powder constituents of a blend granules posses better compressibility and flow properties (Wells et al., 2002; Augsburger et al., 2002; Faure et al., 2001). The process of granules formation or preparation are three stage procedure, such as wetting, nucleation and consolidation and growth followed by attrition and breakage (Lister et al., 2001; Iverson et al., 2001; Faure et al., 2001). During granules formation the wetting or nucleation stage of granules starts when a binding solution or agent is brought into contact with the powder materials to be granulated to form a nuclei (Lister et al., 2001; Iverson et al., 2001; Faure et al., 2001). Then consolidation or granules growth starts after collision between granules. The final stage attrition occurs as a result of wet or dried granular materials fracturing or crumbling due to impact of wear or compaction and subsequent powder handling throughout the manufacturing process (Lister et al., 2001; Iverson et al., 2001; Faure et al., 2001). Like direct compression method this method also has some advantages and disadvantages which are listed in table 2 (Wells et al., 2002; Augsburger et al., 2002).
Chalapathi et al., 2011 in their research focus to enhance safety and efficacy of already available drug. The study was carried out to discover the usage of a natural starch as binding agent in preparation of Diclofenac tablets. Another commonly use of potato and maize starch were selected as disintegrating agents was also explored. All the formulations were compressed using by wet granulation. The evaluation of them proved binding and disintegrating properties.

Wondimu & Gebre-Mariam, 2014 in their study evaluated properties of PCM granules prepared by using wet granulation using pregelatinized starch binder. The properties of PCM granules such as particle size-distribution, flow properties, compressibility were investigated. From the results it was concluded that pregelatinized-enset starch reconstructed in cold water can be used as granulating agent and it can be measured as an important tablet binder in wet granulation method.

Mughal et al., 2011 characterized propranolol HCL-loaded matrix tablets with the help of natural gum, guar gum, xanthan gum, and HPMC as rate-retarding polymers. Tablets were formulated by wet granulation by all mentioned polymers, and granules and tablets were evaluated. Experiential and semi-empirical mathematical models were fit to release data to explain release mechanisms. Guar gum revealed release pattern that matched to Higuchi profile. HPMC gave almost zero-order release for 12 h with erosion.

Jaya et al., 2012 In their work, seven binding agents with wet granulation tech. were used to compress tablets. Seven binders’ viz. PVP, acacia, methylcellulose, sucrose, HPMC, gelatin, and starch were used. The binders based on their disso rate and disso efficiency was acacia>starch>sucrose>PVP>gelatin>HPMC>MC. In general acacia, starch paste, sucrose and PVP were identified to be matching binders for ritonavir tablets.
Table 2.3 Merits & demerits for wet granulation method

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduces air entrapment</td>
<td>1. Each unit process adds complications</td>
</tr>
<tr>
<td>2. Enhances fluidity and compatibility</td>
<td>2. Large numbers of unit processes</td>
</tr>
<tr>
<td>3. Suitable for high does drugs</td>
<td>3. Increases the problems and possible operator errors</td>
</tr>
<tr>
<td>4. Reduces cross contamination and dust</td>
<td>4. Difficult to control and validate</td>
</tr>
<tr>
<td>5. Permits handling of powder without loss of blend quality</td>
<td>5. Potential adverse effects of temperature</td>
</tr>
<tr>
<td>7. Drug stability and distribution during drying</td>
<td></td>
</tr>
</tbody>
</table>

IV. Melt granulation technique

The technique is achieved by usage of meltable binders. Binders having melting point ranging between 50-75°C are preferred. The liquefied binders after melting acts as binder and at normal temperature solidify. The Hydrophobic binder alone some time sufficient in case of SR formulation to retard release; if binder are insufficient to control release, low viscosity hydrophilic polymers can be added that improves release.

Hydrophilic binder can also use to prepare sustain release formulation but they only in formulation are insufficient to release up to 12h or more. Use of sustain release polymer in combination with hydrophilic binder gives desirable sustain release profile.
Table 2.4 Merits & demerits for melt granulation method

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Time and cost effective</td>
<td>1. heat sensitive materials are poor candidates</td>
</tr>
<tr>
<td>effective</td>
<td></td>
</tr>
<tr>
<td>2. control and modifying drug release</td>
<td>2. lower melting point binders get soft on storage</td>
</tr>
<tr>
<td>Good for water soluble candidate</td>
<td>3. higher melting point binder requires high temperature that may affect drug characteristics</td>
</tr>
</tbody>
</table>

Patel et al., 2012 organize and characterize bilayer pill formulation containing antidiabetic drug in extended time release (XR) matrix kind by Melt-granulation and Pioglitazone HCl in immediate release (IR) form for the treatment of diabetes. Completely different formulations containing Met HCl were formulated using $3^2$ factorial styles. The influence of hydrophilic carrier, hydrophobic polymer on drug release was studied. IR layer of Pioglitazone was optimized by completely different super disintegrants. All formulations were evaluated for % drug unleash. Optimization results indicated that unharness rate of drug is directly proportional to the degree of Eudragit S 100 and PEG 6000. Results confirmed that Bilayer pill formulation containing XR of metformin HCl and IR of Pioglitazone HCl may be developed by melt granulation technique.

Sharma et al., 2014 in their study advance SR bilayer matrix formulation that contains 2 anti-diabetic medicaments. Various polymers such as HPMC K15 M, HEC and EC etc. with different strength were used. It was observed that the formulation technique or excipients tried did not modify physical or chemical properties of the medicament, as confirmed by FTIR. Mean DT and regression were resolute to illustrate the drug release rate from formulation.
Wagh et al., 2014, Bilayered metformin HCL as SR and glimepiride as IR tablets were prepared by hot melt-extrusion. Super disintegrants were key factor responsible for IR layer drug release. The use of a hydrophobic & hydrophilic polymer in SR melt-granules formation was the key for SR kinetics. Several mathematical models determined the kinetics of SR layer showed non-fickian mechanism. The technique fruitfully attained the bilayer formulation.
2.5 BILAYERED CONTROLLED RELEASE FORMULATION

Therapeutic methods taking into account oral bilayer (and multilayer) tablets are increasing popularity in market as combination of variables including advances conveyance systems, patient acceptance and blend treatment. Fruitful formulation of these steadily complex frameworks needs to beat series of difficulties from formulation strategy to tablet compression. This article provides an outline of the progressive of bilayer pill technology, revealed the most advantages of this sort of oral formulation forms whereas providing an outline of current challenges and advances toward rising producing practices and formulation quality. Many aspects relevant to bilayer pill producing are self-addressed as well as material properties, lubrication, layer ordering, layer thickness, layer weight management, additionally as 1st and final compression forces. The region fatherly dedicated to bilayer pill characterization that gift additional complexities related to interfaces between layers. The accessible options of the production instrumentation for bilayer pill production also are mentioned indicating the various ways for sensing and controls offered by bilayer pill press makers. Finally, a roadmap for bilayer pill formulation is advanced as a tenet to formulation style and choice of method parameters and instrumentation.

Need for Bi-Layer Tablets

I. For the fixed dose combinations

The fixed dose combination to treat two conditions with atorvastatin and atenolol was carried out by bi-layer tablets. In bilayer tablets, SR layer (10% w/w of xanthan gum and cluster gum) and fast-release layer [1 : three (drug/cyclodextrin)] showed the specified release profile. The pharmacokinetic study illustrated that the quick absorption and hyperbolic oral bioavailability of lipid-lowering medicine similarly as therapeutic concentration of atenolol in blood were made accessible through acceptance of strategy with formulation of bilayer pills (Dey et al., 2014).

Amlodipine/atorvastatin is another once-daily fixed-dose combination for cardiovascular events in hypertensive patients with three concomitant cardiovascular risk factors and/or for hypertension along with dyslipidemia patients. The combination is bioequivalent to both drug given unaided and
doesn't affect efficacy of each other. The convenience of single-pill amlodipine/atorvastatin has the potential to boost patient adherence and therefore the management of cardiovascular risk in selected patients, thereby rising clinical outcomes (McKeage and Siddiqui, 2008). In another formulation valsartan and metformin HCL in FDC had been formulated for dual-phasic release (Dinda et al., 2011)

II. To separate incompatible APIs

FDC of amodiaquine hydrochloride & artesunate delivered challenge in product development due to incompatibility of two drugs. Both drugs create degradation of each other when present together. The study was carried out to develop cost effective stable FDC bilayer tablet with moisture barrier film coating of two incompatible drug amodiaquine hydrochloride and artesunate to increase patient convenience, adherence, and compliance; improve stability and reduce cost of dosage form. Reduced therapy period & pill burden, Improve treatment effectiveness of multidrug resistance in case of falciparum malaria (Modi & Patel, 2011).

In another study bilayer formulation of incompatible drug release amlodipine & losartan was prepared and the stability and drug release issue were overcome. The conventional formulation was locking amlodipine release due to gelation of losartan, formulating them in a separate layer avoid contact of them before release (Pandey et al., 2014; Rama & Bhoot, 2013).

III. Controlling the delivery rate of either single API

Control release of Bilayer tablet formulations with single API, in which both the layer contains same drug but for different release mechanism. Bilayer tablet of Propranolol hydrochloride was developed a using superdisintegrant SSG for the quick release layer and water retarding polymers such as EC, Eudragit RLPO & RSPO for the sustain layer. The formulation successfully releases the drug for 12 hour (Patra et al., 2007). The SR tablets of Isosorbide mononitrate, using MCC PH 101, HPMC K 4 M were prepared. The results showed that formulation was able to sustain the release for 24 h by Bilayer tablet formulations (Pahade et al., 2010). Banu et al., 2011
formulated and developed acetaminophen extended drug release bi-layer tablets.

Sometimes single API in one layer and in the other layer drug release modifier are set for specific purpose like bio-adhesion or floating. Sonar et al., 2007 formulated bilayer floating tablet by altering density approach. HPMC and Na-bicarbonate were added to the floating layer that expands and low density floats, when comes in contact with dissolution media, the tablet remain floating for 8 h and gave continuous release.

IV. **Controlling the delivery rate of two different APIs**

Here in these types of bilayer tablets formulations, two different API that intended to release IR and SR in separate layer or both in SR release. Kesarwani et al., 2006 prepared extended release tablets of Metformin and Glipizide for treatment of NIDDM patients on a once-a-day basis and provides therapeutically effective plasma levels of both drugs for a period of at least 12 hours, particularly 24 hours. Pattanayak et al., 2011 developed bilayer tablet containing Metformin as SR layer and Glimepiride in IR layer different types of as polymers were used in order to get the prolonged hypoglycemic effect period of 24 h.
2.6 PREFORMULATIONS & EXCIPIENTS

2.6.1 SIMULTANEOUS ESTIMATION

Simultaneous estimation plays a really vital role in pharmaceutical world because it is incredibly possible and time saving. For the multi part analysis numerous techniques like spectrophotometric techniques (UV-VIS, IR, NMR and MASS spectrometry) and activity techniques (Thin Layer activity, High Performance Liquid activity, Ultra-High Performance Liquid activity) is employed. These techniques offer high degree of specificity and property and any offer the high degree of assurance that these techniques fit the coincidental estimation of the pharmaceutical indefinite quantity type. activity and spectrophotometric techniques along develop new combined techniques that square measure helpful for the coincidental estimation and impurity identification. The coincidental analytical analysis provides specificity and make sure for the identification of the content within the dosage formulation. the most objective behind the analytical estimation is to supply the reassurance that the actual formulation contains the equal quantity of active pharmaceutical ingredient as mentioned within the label.

The AUC methodology for coincidental estimation of paracetamol (PARA) and nabumetone (NAB) in bulk and pill dose type. AUC methodology includes determination of space of PARA and NAB at absorption maxima, that for PARA was 248.8 ± ten nm and for NAB was 269.2 ± twm nm. Beer's law was obeyed within the concentration vary of five-twentyfive $\mu$g/mL for each PARA and NAB. Correlation was found to be 0.9983 and 0.9993 for PARA and NAB, respectively for area under curve methodology. The mean percent recoveries were found satisfactory for the projected methodology. The percentage recovery was found to be 101.67–102.43% for PARA and 96.69–98.49% for NAB. The projected AUC methodology used for the coincidental estimation of PARA and NAB in bulk and pill dose type severally (Rote et al., 2012).

Mane et al., 2011, in another study versatile, accurate, precise and economic technique for simultaneous determination of lipid-lowering medication and ezetimibe in mounted dose combination product was developed. This technique obeyed Beer’s law within the concentration vary of 3–18 $\mu$g /ml for lipid-lowering medication and 5-
30 µg/ml for ezetimibe. The results of analyses are valid statistically for one-dimensionality, accuracy and exactitude, LOD and LOQ of the planned technique.

Abdelwahaba et al., 2012 carried out two different technique for simultaneous determination of Lipitor Ca (ATR) and Ezetimibe (EZ) in their bulk powder and pharmaceutical dose form. technique (I) relies on twin wavelength analysis whereas technique (II) is that the mean centering of magnitude relation spectra spectrophotometric (MCR) technique. In technique (I), 2 wavelengths were selected for every drug in such the simplest way that the distinction in absorbance was 0 for the another drug. At wavelengths 226.6 and 244 nm EZ had equal absorbance values; so, these 2 wavelengths are used to verify ATR; on an analogous basis 228.6nm & 262.8nm were obtained to determine EZ in their binary mixtures. In technique II, the absorption spectra of each ATR and EZ with totally different concentrations were recorded over the vary 200–350, divided by the spectrum of appropriate divisor of each ATR and EZ so the obtained magnitude relation spectra were mean targeted. The concentrations of active parts were then determined from the calibration graphs obtained by measure the amplitudes at 215–260 nm (peak to peak) for each ATR and EZ. Accuracy and precision of the developed ways are tested; additionally recovery studies are distributed so as to verify their accuracy. On the opposite hand, selectivities of the ways were tested by application for determination of totally different or various artificial mixtures containing different ratios of the studied medication. The developed ways are with success used for determination of ATR and EZ in their combined dose kind and applied mathematics comparison of the developed ways with the reported spectrophotometric one using F and Student's t-tests showed no important distinction concerning each accuracy and preciseness.

2.6.2 PRODUCTION WITH POORLY SOLUBLE DRUG

Solubility is dissolution of solid in liquid part to grant an even system. Solubility is one of the necessary parameter to attain desired concentration of drug in circulation for medical specialty response to be shown. Poorly water soluble medication often need high doses so as to succeed in therapeutic plasma concentrations when oral administration. Low liquid solubility is major downside encountered with formulation development of latest chemical entities. Any drug to be absorbed should be available
within the sort of time in solution at the location of absorption. Water is solvent of selection for liquid pharmaceutical formulations. Most of medication weak acidic and weak basic with poor liquid solubility, thus numerous techniques are used for the development of the solubility of poorly soluble medication embody micronization, chemical modification, pH scale adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Various techniques of solubilizaton are being used for the attainment of effective absorption and enhanced bioavailability.

Rao et al., 2001 found that Sustained-release preparations using hydrophilic matrix for poorly water-soluble active frequently end in insufficient release due to its poor solubility and dissolution rate in the matrix. The author used beta-cyclodextrins (beta-CDs) that is used to improve the solubility of such drugs by forming inclusion complexes. In the study modification of less water-soluble API, was tackle using Sulfobutylether-beta-cyclodextrins (SBE)(7M)-beta-CD as a solubilizing agent was carried out. PDL, (SBE)(7M)-beta-CD, and polymer were mixed physically and tablets were made ready by directly compressed. On the bases of drug release of controlled formulation (without beta-CD) over PDL:(SBE)(7M)-beta-CD complex, it showed higher water uptake relative to the control formulation. The study thus proved that incorporation of beta-CD into the matrix tablets was successful in designing a SR tablet of poorly water-soluble drugs.

Gan at al., 2002 developed CD complex diffusion pill for Glipizide delivery. Here poorly soluble Glipizide was selected because the model drug to organize diffusion pump tablets with correct added material once it had been created an inclusion complex by kneading technique so as to extend solubility. PEG 4000 and cellulose ester were selected because the coating materials, and acetone–water (95:5) co-solvent was utilized because the coating medium. The drug unleash profile of the best formulation was compared with a commercialised push–pull diffusion pill. The results indicated that glipizide–cyclodextrin inclusion complex choose had glorious zero-order unleash characteristics in vitro.

Serajuddin, 1999, commercialised use of solid dispersions of medicine that is mostly produced by melt or solvent evaporation ways. The materials, that were sometimes
solid and waxy in nature, were hardened by cooling to terribly low temperatures. They were then powdered, sieved, mixed with comparatively massive amounts of excipients, and encapsulated into onerous gelatin capsules or compressed into tablets. These operations were tough to scale up for the manufacture of dose forms. the case has, however, been dynamical in recent years as a result of the provision of surface-active and self-emulsifying carriers and therefore the newer techniques to encapsulate solid dispersions mixture into onerous gelatin capsules. Solid plugs area unit formed within the capsules once the melts area unit cooled to temperature. as a result of surface activity Some sensible limitations of dose form development could be the inadequate solubility of medicine in carriers and therefore the instability of medicine and carriers at elevated temperatures necessary to manufacture capsules.

2.6.3 KINETICS OF MEDICAMENT RELEASE

Over recent years, API dissolution from solid pharmaceutical dosage forms has been the topic of powerful and moneymaking systematic expansions. Whenever a brand new solid dosage form is developed or created, it's necessary to make sure that drug dissolution occurs in an appropriate manner. The pharmaceutical business does focus, nowadays, on drug dissolution studies. The qualitative analysis of the values obtained in dissolution tests is less complicated once mathematical formulas that detailed the dissolution results as a function of a number of the dosage forms characteristics can be used. For few, these models are obtained from the theoretical analysis of the occurring method. In most of the cases the theoretical conception doesn't exist and a few empirical equations have well-tried to be a lot of applicable. Drug dissolution from solid indefinite quantity forms has been delineated by kinetic models within which the dissolved amount of drug (Q) could be a operate of the test time, t or letter of the alphabet five f(t). Some analytical definitions of the Q(t) operate are unremarkably used, like 0 order, 1st order, Weibull, Hixson–Crowell, Baker–Lonsdale, Higuchi, Hopfenberg and Korsmeyer–Peppas models, alternative unleash parameters, like dissolution time (tx the concerns), assay time (tx min ), dissolution effectiveness (ED), distinction factor ( f1 ), similarity issue ( f2 ) and Rescigno index ( j1 and j2 ) can characterize drug dissolution / unharness profiles (Costa & Lobo, 2001)
Vendruscolo et al., 2005, formulated theophylline tablets, containing (Keltrol ®) (X) and an extremely deliquescent galactomannan (G) from the seeds of Mimosa scabrella (a brazilian herbaceous plant tree known as bracatinga) as release-controlling agents, were obtained. Knowledge from the in vitro drug unleash were analyzed by completely different equations and kinetic models so as to judge the discharge mechanism of theophylline from the matrices. The software package SPSS version ten.0 were used. The XG matrices were able to manufacture close to zero-order drug unleash. The XG(SD) tablets provided the desired unleash rate (about 90% in 8 h), with zero-order unleash kinetics. Tablets containing G(VO) in low concentration showed an entire erosion, whereas the others demonstrated quick hydration and swelling when get contacted with liquid medium. Both diffusion and relaxation was observed for release. The relative importance of those 2 processes varied with matrix composition. The XG(SD) V-E Day matrix showed higher contribution of compound relaxation.

2.6.4 FORMULATION OPTIMIZATION

The acceptable and desirable pharma-formulation in minimum likely time via minimum of man power and excipients are possible now days. Conventionally formulations were developed by varying one changeable at a time method. The method needs time and requires a tremendous of creative efforts. Further, to progress a model formulation by this classical technique may be difficult as the mixture impact of independent variables are not taken in to account. So it is very important to recognize the involvedness of formulation by consuming well recognized statistical-tools like factorial design. This system of factorial design is an impressive method representing the comparative importance of a number of changeable components of system and interactions between them. Depending upon independently changeable components selected in the system, the no. of experiments are decided and for each experiment determination of Yi, (responses) carried out (shah et al., 2013).

Madan et al., (2009) investigated FDT of Aloe and this innovation was optimized by a 3² fullfactorial design and mix effect of two changing components of system - quantity of mannitol and Avicel were investigated. The multiple-regression analysis showed an optimal best concentration of mannitol and a good quantity of MCC can
give good results. A 2D plot was delivered to signify the outcome of variables on the wetting time and disintegration time. Next to it generation of scientific calculation model and its validation by preparing a check point formulation.

Celebi et al., (1996) prepared Salbutamolsulphate multiparticulate system using poly(lactic-acid-co-glycolic acid). In the study a $2^3$ factorial project was tried with amount of gelatin, drug loading, and polyvinyl acetate as independent changeable components. The entrapment ratio and particle size were chosen as dependent changeable components. The effects of changeable components were estimated with ANOVA and response-surface graphs.

Gohel et al (1998) in his study, explore factorial design with the influence of three variables: % of liquid-paraffin (blend of heavy and light in the dispersion medium (X3) concentration of Calcium-chloride (X2), and the stirring-speed (X1) on the time (t) for drug dissolution 80% (t80) as dependable variables were selected. The significant terms were selected from model 2D amd 3D curves were prepared for t80. Anomalous diffusion kind release was identified by kinetic studies. The generated model was authenticated for its accurate forecast of drug-release profile.

Li et al (2003) in his investigation employed $2^3$ full factorial designs to examine the effect of design variables on dependent variables, drug release and floating properties of the delivery system. HPMC of different viscosity grades and Carbopol 934P as independent variables were used for framing the gastric floating drug delivery system. A mathematical model was used to check quantitatively the main effects and interaction terms. The study revealed that HPMC-viscosity, the presence of Carbopol and their interaction had important influence on the release and floating properties. The reduction in drug release rate was detected with a surge in the viscosity of the polymeric system.
2.6.5 PHARMACOKINETIC STUDY

I. In vitro study

Kinetics of Drug Release and its Mechanism

To analyze drug release rate kinetics of optimized dosage form, the graphs were plotted as:

- Zero order plots: % CDR vs. Time
- First order plots: Log %CDUR vs. Time
- Higuchi’s plots: % CDR Vs. \( \sqrt{\text{time}} \)
- Hixson-Crowell Model: \( \sqrt[3]{\text{unreleased drug}} \) Vs. time
- Peppas plots: Log % CDR vs. Log time

Here % CDR indicates drug release in cumulative fashion in% and %CDUR indicates drug unreleased in cumulative fashion in%

A. Zero Order Release Rate Kinetics (Donbrow et al., 1980)

The equation for zero order treatment is represented as

\[
Q_t = K_0 \times t
\]

Where, \( K_0 = \text{zero order release constant} \)

\( Q_t = \% \text{ CDR} (t) \)

When the data is plotted as % CDR versus time, if the plot is straight line then the data obeys zero order release kinetics, with a slope equal to \( K_0 \).

B. First Order Kinetics (Lapidus & Lordi, 1966)

The equation for first order treatment is represented as

\[
Log Q = Log Q_0 - K_1
\]

Where, \( K_1 = \text{first order rate constant} \)
\( Q_0 = \) initial amount of drug in solution
\( Q = \) amount of unreleased drug remaining at time \( t \)

The data plotted as cumulative percent drug retained versus time yields a straight line; if straight line obtained it specifies that first order the release kinetics is followed. The constant \( K_1 \) can be obtained by multiplying 2.303 with slope values.

C. Higuchi Release Model (Higuchi, 1961, 1963)

The simplified Higuchi equation is represented as

\[
Q_t = K_H \times \sqrt[3]{t}
\]

Where, \( K_H = \) Higuchi’s constant

\( Q_t = \%\) CDR in time \( t \)

If a linear relationship between \( Q \), amount of drug released and \( \sqrt{\text{time}} \) is observed, the drug release from the matrix will be diffusion controlled.

D. Hixson-Crowell Model (Hixon & Crowell, 1931)

The simplified equations is represented as

\[
\frac{3}{\sqrt[3]{Q_0}} - \frac{3}{\sqrt[3]{Q_t}} = K_S t
\]

Where, \( Q_0 = \) initial amount of drug in solution \( K_S = \) cube–root constant

\( Q_t = \%\) CDR in time \( t \)

A graphic representation of \( \sqrt[3]{\text{unreleased drug}} \) versus time will be linear whenever regular shape of the formulation reduces with time.

E. Korsmeyer and Peppas Release Model (Korsmeyer et al, 1983)

The korsmeyer peppas model relates drug release exponentially to time. It is described by the following equation (Korsmeyer and Peppas, 1981)
\[ \frac{M_t}{M_\infty} = K_t^n \]

Where, \( \frac{M_t}{M_\infty} \) = fractional release of drug

\[ n = \text{release exponent} \]

\[ K = \text{constant} \]

The value of \( n \) indicates the drug release mechanism. This model is used to analyze the release of drug from polymeric dosage forms, when release mechanism is not understood or when there is a possibility of more than one type of release mechanisms are involved and to study the release kinetics, log cumulative percentage drug release versus log time linearity is to be observed.

### Table 4.5 Interpretation of Matrix Release Mechanism

<table>
<thead>
<tr>
<th>Release Exponent (n)</th>
<th>Drug Transport Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>Fickian Diffusion</td>
</tr>
<tr>
<td>0.5</td>
<td>Fickian Diffusion Pure</td>
</tr>
<tr>
<td>0.5 &lt; n &lt; 1.0</td>
<td>Non-Fickian</td>
</tr>
<tr>
<td>0.5-0.85</td>
<td>Anomalous</td>
</tr>
<tr>
<td>0.85</td>
<td>Dissolution</td>
</tr>
<tr>
<td>&gt;0.85</td>
<td>Zero order (dissolution controlled)</td>
</tr>
<tr>
<td>1.0</td>
<td>Case-II transport</td>
</tr>
<tr>
<td>n&gt;1.0</td>
<td>Super Case-II</td>
</tr>
</tbody>
</table>

### II. Invivo study

The assessment of preclinical in vivo information of important compounds could be a necessity for regulatory, succeeding toxicology studies and selections on a clinical drug candidate within the drug development method. Information generated
in relevant species like mouse or rat backing the prediction of metabolism or PK in humans and might facilitate to seek out higher formulations or new therapeutic applications for existing medicine.

**In Vivo Assays**

In preclinical-pharmacokinetics, oral or IV studies on rat and mouse can be carried out to determine,

- Half-life
- Clearance
- Volume of distribution
- Bioavailability

**Factors that determines the invivo act of SR formulations (Jaber & Naser, 2004)**

I. **Physiological**

- GI blood flow
- Prolonged-drug absorption
- Influence of feeding on drug absorption
- Variability in GI emptying and motility

II. **Pharmacokinetic/ biochemical**

- Inconsistency in urinary pH;
- Dose dumping
- Effect on drug removal
- Enzyme inhibition / induction upon multiple dosing
- First- pass metabolism

III. **Pharmacological**

- Sensitization/ tolerance
- Changes in drug effect upon multiple dosing

Liu and Chen, 2003 formulated MOTS The relative bioavailability and human pharmacokinetics of formulated nifedipine MOTS were carried out and matched with an equivalent dose, marketed Adalat® osmotic system following an oral 1 dose of 30 mg to every 11 healthy volunteers in in vivo, randomized, an open crossover study.
The results showed that developed system is feasible for a long-acting treatment as a once-daily preparation.

Nie et al., 2007 carried out pharmacokinetics studies of controlled release BOPT containing allopurinol and also oxypurinol (active metabolite) The study of two-preparation was carried out by two-period crossover manner relative to the equal dose of market available allopurinol formulation and were evaluated invivo in six Beagle dogs. The results revealed that allopurinol BOPT provide a slow and controlled release of both medicaments.