6. Literature review

6.1 Literature review matrix

Taha E. et al (2015) evaluated Diclofenac Sodium (DS) matrix tablets prepared by direct compression method under different compression forces using ethyl cellulose as matrix forming material. The produced tablets were characterized for hardness, friability, drug content, weight variations and in vitro drug release. Incompatibility study carried out using DSC FT-IR spectroscopy and XRD. It revealed from data that on increasing compression force the in vitro drug release was sustained as compared to the conventional marketed tablet\(^6\).\(^9\)

Khan R. et al (2014) formulated and evaluated Rabeprazole sustained release matrix tablet using wet granulation technique incorporating various polymers like HPMC-E15, Carbopol934, and sodium carboxymethyl cellulose (CMC). The formulated tablets were evaluated for different physicochemical properties like rheological properties, weight variation, thickness, hardness, percent friability, in vitro release studies and drug content. Studies revealed that all the physicochemical parameters comply with the official standards. The in vitro release studies exhibits the release up to 90\%, over a prolonged period of time which confirms the extended release profile of formulation, having better bioavailability as well as decreased dosing frequency with reduced doses\(^7\).\(^0\)

Sharma P. et al (2013) developed matrix tablets of nateglinide in combination with the polymers hydroxypropylmethylcellulose (HPMC), Eudragits, ethyl cellulose and polyethylene oxide and the formulated drug release patterns were evaluated using in vitro and in vivo studies. The formulation contained 15\% HPMC K4M having sustained release profile and was found to be stable at accelerated storage conditions for 3 months with respect to drug content and physical appearance. In-vitro release studies and pharmacokinetic in vivo studies in rabbits confirmed the sustained drug release profile\(^7\).\(^1\)

the potential for developing sustained release Diclofenac sodium tablets, using Compritol 888 ATO as a lipid matrix, by a wet granulation technique. Rapid release of Diclofenac sodium from directly compressed matrices was observed. A wet granulation technique using different HPMC binders produced free-flowing granules and matrices which released Diclofenac sodium in a sustained manner over several hrs. Release rates were consistent over a range of compression speeds and forces indicating the suitability of the formulation for production on a rotary tablet press\textsuperscript{72}.

Li L. et al (2013) focused on the formulation optimization of metoprolol succinate sustained release tablets using hydroxypropyl methylcellulose (HPMC) and sodium alginate (SA) as the matrix combination. 5-level central composite design was employed, using the amount of HPMC K4M (A) and SA (318 cP) (B) as the independent variables and the drug percentage released at 1, 4, 8, and 20hrs (Q1, Q4, Q8, Q20) as the responses. This matrix combination is good alternative to the commercially pellet technology, which was complicated, time-consuming and energy-intensive\textsuperscript{73}.

Qazi F. et al (2013) develop a sustained release hydrophilic matrix tablet of Diltiazem HCl and evaluates the effect of formulation variables (e.g. lubricant, binder, polymer content and viscosity grades of HPMC) on drug release. Rate of drug release was found to be slow as the fraction of the polymer was increased. The drug release rate from tablets containing HPMC K4M was effectively controlled by increasing the talc concentration, whereas the burst effect was reduced by increasing binder content\textsuperscript{74}.

Ali A. et al (2013) carried out development of oral sustained release tablets of Propranolol HCl using different ratios of drug:matrix. Tablets were prepared by direct compression technique using xanthan gum and lactose. All the formulations (tablets) were evaluated for thickness, diameter, hardness, friability, weight variation, content of active ingredient, in vitro dissolution using USP dissolution apparatus-II and swelling index. In case of dissolution, an inverse relationship was noted between amount of xanthan gum and release rate of Propranolol HCl and the drug release was gradually enhanced as the amount of the lactose increased.\textsuperscript{75}.
Baviskar D. et al (2013) examined the effect of hydrophilic, plastic and hydrophobic types of polymers and their content level on the release profile of drug from matrix systems. To improve therapeutic efficacy, systemic absorption and patient compliance a sustained release matrix tablets of Verapamil HCl (VHE) has been developed. VHE tablets were prepared by using various polymers like hydrophilic (HPMC K100M), plastic (Kollidon SR), hydrophobic (Eudragit RSPO) and combination of best two resulted polymers using direct compression. A good correlation between the dissolution profiles and bioavailability indicated a linear relationship between in vitro - in vivo data. The current study attained the successful design, development and optimization of controlled release once-a-day formulation of VHE.

Al-Akayleh F. et al (2013) described development of a sustained release of terbutaline sulfate tablet (TBS) and optimized by employing the hydrophilic polymers; chitosan and xanthan gum mixed with sodium bicarbonate as a release modifying agent. This formulation was developed using direct compression technology. In vitro release studies indicated rapid swelling and drug release in the initial period of the acid stage from a matrix composed of chitosan and xanthan gum solely. Various formulation factors such as polymer to polymer ratio, polymer viscosity and particle size were altered and their effect on dissolution pattern was illustrated. Manufacturing variables such as compression force and lubricant percentage were investigated and found not to influence the drug release profile of the resulted tablets. The release profiles were analyzed using statistical method (one-way ANOVA) and f2 metric values and found to be similar to the commercial product. Reproducible data were obtained when scale-up of the formulation was performed.

Chaibva F. et al (2012) focused on sustained release of salbutamol sulfate using hydrophilic matrix polymer. A central composite design was used as the framework for manufacturing formulations that may be used to understand the relationships between polymer levels and in vitro release characteristics. Tablets were manufactured using wet granulation with Surelease as the granulating fluid and different levels of Methocel K100M, xanthan gum, and Carbopol 974P as matrix-forming materials. The results revealed that the levels and types of polymers had a significant impact on the rate of drug release from these formulations and that it was possible to optimize the levels of
matrix-forming polymers to achieve the desired release characteristics. Statistical design and response surface methodology have been successfully used to understand and optimize formulation factors and interactions that impact the in vitro release characteristics of salbutamol sulfate from a potential multisource sustained release dosage form\textsuperscript{78}.

**Mughal M. et al (2011)** characterized propranolol hydrochloride-loaded matrix tablets using guar gum, xanthan gum, and hydroxypropylmethylcellulose (HPMC) as rate-retarding polymers. Tablets were prepared by wet granulation using these polymers alone and in combination, and physical properties of the granules and tablets were studied. Drug release was evaluated in simulated gastric and intestinal media. Rugged tablets with appropriate physical properties were obtained. Empirical and semi-empirical models were fit to release data to elucidate release mechanisms. The results confirm that guar gum, xanthan gum, and HPMC can be used for the successful preparation of sustained release oral propranolol hydrochloride tablets\textsuperscript{79}.

**Ceballos. A. et al (2005)** revealed that sustained release matrix tablet of Theophylline were prepared by direct compression using different types of methacrylates. The influence of varying the polymer/polymer (w/w) ratio and the drug incorporation method was evaluated. Tablets with a 0.7:0.3 w/w mixture of Eudragit L100-Eudragit RLPO showed highly reproducible drug release profiles and allowed 100% released drug after 360 min\textsuperscript{80}.

**Ning W. et al (2005)** describe the transport phenomena of water soluble drug caffeine from poly ethylene oxide tablets using mathematical modeling. In vitro studies on swelling, dissolution behavior of PEOs with different molecular weights and drug release were carried out. Drug release profiles using this model are predicted with a very good agreement with experimental data and the overall drug release process is found to be highly dependent on the matrix swelling, drug and water diffusion and polymer dissolution\textsuperscript{81}.

**Shahla J. et al (2006)** depicted a monolithic matrix system for glipizide using hydroxypropyl methylcellulose and poly ethylene oxide. The interrelationship between
matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions showed promising sustained release effect\textsuperscript{82}.

**Atul K. et al (2006)** reported extended-release matrix tablets of zidovudine formulated using hydrophilic Eudragit RLPO and RSPO alone and in combination with hydrophobic ethyl cellulose. The in-vitro drug release studies and in vivo 46 investigations in rabbits were carried out. The results indicated the prepared tablets of zidovudine are effective than conventional systems, with improved efficiency and patient comfort\textsuperscript{83}.

**Per B. et al (2006)** employed model for the drug release from matrices and used to study the influence of the drug diffusion coefficient, the drug solubility and the initial drug loading on the drug release profile. The model is verified against drug release data and polymer dissolution data for drug loaded PEO tablets, for a drugs methyl paraben and a saligenin\textsuperscript{84}.

**Celine V. et al (2006)** described the effects of particle size, viscosity and chemical composition of alginates on drug release from alginate matrix tablets using Chlorpheniramine maleate as model drug. The results showed that sodium alginate matrices can sustain drug release for at least 8 hrs, even for a highly water-soluble drug in the presence of a water soluble excipient\textsuperscript{85}.

**Varshosaz J. et al (2006)** examined sustained release of tramadol hydrochloride from tablets prepared using natural gums like xanthan and guar gum, and with the hydrophilic matrices of HPMC and CMC. The prepared tablets were evaluated drug release patterns and for polymer hydration. The results showed that guar gum only cannot extend the drug release for prolonged period of time, while xanthan gum along various other polymers extended the drug release for an extended period of time\textsuperscript{86}.

**Sandra F. et al (2006)** studied the effect of the types of diluent and the diluent to matrix ratio on the drug release behavior from both lipophilic and hydrophilic matrix tablets was studied using Ketoprofen, theophylline and sodium sulphadiazine as model drugs. The results obtained with the three examined drugs explained the role of the
drug solubility in determining the influence of formulation parameters on drug release rate from the matrix tablets\textsuperscript{87}.

**Thawatchai P. et al (2008)** explored effect of formulation variables on drug release from the prepared three layered sustained release matrix tablets of Chlorpheniramine maleate prepared by hot-melt extrusion containing chitosan–xanthan gum as matrix materials. The drug release exhibited pH and buffer species independent attributable to slow media uptake into tablet that resulted from the molten state of preparation process and the interand intra-molecular hydrogelation of the matrix materials\textsuperscript{88}.

**Hongtao L. et al (2008)** carried out the study of drug solubility on polymer hydration and drug dissolution from modified release matrix tablets of PEO using Acetaminophen and Ibuprofen as model drugs. Delayed drug release was attributed due to the formation of hydrogel layer on the surface of the tablet and the penetration of water into matrix core through drug dissolution and diffusion\textsuperscript{89}.

**Praveen S. et al (2008)** formulated matrix tablet of rifampicin and isoniazid combination using hydrophilic polymers HPMC, HPC and Eudragit L100 to study the design parameters and to evaluate in vitro release characteristics. Formulations containing 80\% HPC and 60\% Eudragit were found to be of ideal and provided required sustained release profile for both Rifampicin and Isoniazid\textsuperscript{90}.

### 6.1.1 Conclusion

The matrix tablet prepared by direct compression has brought much attention due to its technical and industrial production simplicity in comparison with other controlled release systems. It required fewer unit operation processes, less machinery, reduced number of personnel, less processing time, improved product stability and increased production rate. For sustained release systems, the oral route of drug administration has, by far, received the most attention as it is natural, uncomplicated, convenient and safer route.

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility. The formulation of matrix tablets by direct compression is a cost saving simple process. Polymers utilized as hydrophilic excipients for controlled
release formulations (i.e. HPMC, alginates, xanthan gum) are well known and widely used. The major benefits of matrix sustained release formulation are optimization of drug delivery rate by programmed release into systemic circulation in order to achieve an appropriate pharmacodynamic response. This leads to product safety and reduce the extent and incidence of major adverse drug reactions due to a control of drug level in blood
6.2 Literature review hot melt technique

Hasa D. et al (2011) prepared helical and cylindrical extrudates by melt extrusion and to evaluate their potential as sustained release dosage form using theophylline as water-soluble model drug and microcrystalline wax as thermoplastic binder. The temperature suitable to ensure a successful extrusion process of formulations containing the wax in three different percentages was found to be below the melting point of the excipient. The different systems were analyzed from the in vitro dissolution point of view to study the influence of the shape and of the composition on the drug release and in vivo pilot study on the best performing system (helix with 3 blades) was carried. The result proves that the drug release sustained both in vitro and in vivo\textsuperscript{91}.

Al-Zein H. et al (2011) described a sustained release tablet for a drug which has poor solubility in alkaline medium using complexation with cycloextrin. drug solubility in the intestinal media was improved by forming binary system NC-HPbCD and later embedded the complexed drug into a plastic matrix, by fusion method by using PEG 4000. The prepared solid dispersion was mixed with other excipients, avicel PH101, lactose, and talc for extended release dosage forms. The kinetics of the release showed that the diffusion is the major factor controlling the drug release. The prepared waxy matrix tablet shows promising results as extended release tablets\textsuperscript{92}.

Ahmed et al developed sustained release matrix tablet of diclofenac sodium (DS) using carnauba wax (CW) as a matrix former, in addition, polyethylene glycol (PEG 6000) and polyvinyl pyrrolidone (PVP K30) were used as channeling agents to modify and control the release of DS from CW based matrix system. The release rate of DS from CW based matrix system was affected by many factors including the concentration of the rate retarding polymer, type and concentration of the channeling agent used, type of filler used, pH of the medium, compression force and method of preparation of the sustained release granules. Carnauba wax-polyethylene glycol system can be used successfully as a matrix former to sustain the release of DS to more than 8hrs \textsuperscript{93}.

Takka S. et al (1998) studied the release rate of Nicardipine HCl from various alginate gel bead formulations prepared by \(3^2\) factorial design. The effect of drug-polymer weight ratio, \(\text{CaCl}_2\) and sodium-alginate concentration on the time for 50\% of the drug to be released (t) and the drug entrapment efficiency were evaluated with analysis of
variance (ANOVA). The release of Nicardipine was extended with the alginate gel beads and the release was due to the diffusion and erosion mechanism at pH 7–7.5\textsuperscript{94}.

**Bhisaid S. and Hasan A. (1980)** depicted the release of aminophylline and theophylline embedded in a matrix composed of different ratios of microcrystalline cellulose and glyceryl monostearate. The result indicated that drug release within a certain period follows a diffusion-controlled matrix model, where the drug quantity released was proportional to the square root of time. The release rate was found to increase with increasing microcrystalline cellulose-glyceryl monostearate ratio. The tablets prepared using solvent-evaporated matrix showed quicker release than those prepared from fused ones\textsuperscript{95}.

**Dakkuri A. et al (1978)** determined the influence of several surfactants on the in vitro release of tripelementamine hydrochloride from a wax matrix. The congealed mass, prepared by dispersing the drug and surfactant in a molten mixture of carnauba wax and stearyl alcohol, was granulated and compressed into cores. Water-insoluble surfactants had no effect on the dissolution rate; slightly soluble agent moderately increased dissolution. However, the water-soluble agent considerably increased the dissolution rate. The data suggest that a surfactant may make more channels available for the dissolution fluid to leach out the drug\textsuperscript{96}.

**Frank W. et al (1974)** characterized the release of drug from a wax matrix tablet under relatively mild agitation conditions. It was found that phenylpropanolamine hydrochloride was released from a typical wax matrix by a diffusion mechanism. After an initial rapid release of drug from the tablet, the amount dissolved was proportional to the square root of time. Data on drug release from a single tablet face compared to release from a totally exposed tablet indicated that drug release is proportional to the total surface area\textsuperscript{97}.

**Hasan Al-Shora et al (1980)** formulated and evaluated sustained release theophylline tablets constituting carnauba wax, and PEG were prepared using fusion or solvent evaporation. This channeling agent increased the release rate according to its concentration and molecular weight. Tablets prepared through fusion technique achieved quicker release than those prepared by solvent evaporation. At a certain
period of dissolution, the drug release processed by zero-order process; this period was
dependent on channeling agent concentration\textsuperscript{98}.

**Adnan Dakkuri et al (1978)** employed povidone as a channeling agent in the
formulation of a sustained-release tripelennamine hydrochloride. Release was
significantly influenced drug release over 10 hrs. The results obtained from cores made
by double compression of the dry-blended ingredients indicated that fusion is essential
for channel formation. A decrease in the release rate was obtained when the polymer
was included in the dissolution medium\textsuperscript{99}.

**Pallagi E. et al (2004)** developed iron sulfate containing lipophilic matrices were by a
special hot-melt technology (melt solidification in drops), using stearin, white wax and
their mixture as conventional bed materials. In all probability, the release of the active
agent can be regulated through the use of a melt of stearin and white wax in different
ratios. The development products functioned as a sustained-release system and ensured
elimination of the irritation of the gastric mucosa. At the same time, the results justified
the applicability of the special hot-melt technology in the development of the solid
dosage form\textsuperscript{100}.

**Hans G. et al (1978)** developed phase diagrams of binary mixtures of tripelennamine
HCl and tolazoline HCl with carnauba wax and castor wax showed a slight depression
in the drug melting point. For ternary systems, i.e., drug, carnauba wax, and stearyl
alcohol, thermograms of samples prepared by a fusion method differed slightly from
those obtained with mixtures formulated by dissolving all ingredients in chloroform
and evaporating the solvent. The phase diagrams suggest that the combinations are
strictly physical and that it is the physical characteristics, such as the hardness and
composition of the core and drug particle size, that influence the release or dissolution
of the drug from the waxy matrix\textsuperscript{101}.

**Shady M. et al (2010)** studied the control release of freely water-soluble salbutamol
sulphate (SS) over a prolonged period of time by embedding the drug into slowly
eroding waxy matrix materials such as Precirol ATO 5, Compritol 888 ATO, beeswax,
paraffin wax, carnauba wax, and stearyl alcohol. The matrices were prepared by either
direct compression or hot fusion techniques. The hot fusion method was found to be
more effective than the direct compression method in retarding SS release. The hydrophobic matrix system is thus a useful technique for prolonging the release of freely water-soluble drugs such as salbutamol sulphate102.

**Balamurugan J. et al (2012)** studied novel sorbitol based extended release tablets by melt dispersion method using carbamazepine as a model drug. Carbamazepine was melted along with sugar alcohol to get Melt dispersion granules. The release rate was found to be affected by sugar alcohol concentration, particle size of granules, the nature of co-excipients, agitation rate and hardness. It can be concluded that sorbitol is a suitable matrix-forming agent to sustain the release of low soluble drug carbamazepine. Melt dispersion technique proved to be a promising technique for controlled drug delivery103.

**Dredan J. et al (1998)** investigated the effect of various types and amounts of polysorbates on potassium chloride release. Potassium chloride, which is a highly water-soluble model drug, was embedded into wax (containing surfactants) to produce a sustained-release dosage form. The application of polysorbates in more than 2% concentration did not alter either the release rate of the embedded potassium chloride, or the surface tension values of the aqueous solutions. The results of this study allow the determination of the optimal concentration of polysorbates in the case of the potassium chloride release104.

**Dipak S. et al (1990)** prepared Tablets using theophylline, lactose and Precirol by a granulation technique, resulting in more than 12 hrs release. Granulation and hot fusion methods were used to prepare admixtures of quinidine gluconate and Precirol at different ratios of. Dissolution studies in 0.1N HC1 showed drastic differences in the release of quinidine gluconate from tablets made by the two different methods; granulation method gave a faster release while the hot fusion method gave slower and incomplete release at higher Precirol content. The release rate decreases with higher Precirol content105.

**Sudha B. et al (2010)** investigated hydrogenated cottonseed oil (HCSO) as a sustained release matrix for a freely soluble drug, Tramadol. A hydrophobic matrix tablet of Tramadol was prepared by compression of physical mixture of drug and wax, disperse
in HCSO by hot fusion techniques. The method of preparation of tablet had a significant effect on drug release with higher release observed from direct compression matrices and slower release from matrix prepared by dispersion (hot-fused matrices). NaCMC was effective at a lower ratio and when incorporated at higher level made HCSO matrix to erode and disintegrate in a short period\textsuperscript{106}.

**Aiman A. et al (2001)** developed inert matrix to control the release of Tramadol HCl. The inert matrix was prepared using glyceryl behenate as a matrix forming agent. The matrices were prepared by either direct compression of a physical mixture of the drug and the matrix forming agent or by compression of the granules prepared by hot fusion of the drug and the matrix forming agent. The hot fusion method was found to be more effective than compression of physical mixture in retarding the release of the matrix. This study showed that glyceryl behenate is an appropriate waxy material that can be used as a matrix forming agent to control the release of a water soluble drug such as Tramadol HCl\textsuperscript{107}.

**Senel S. et al (1991)** studied influence of several formulation factors on the release kinetics of potassium chloride from directly compressed matrices. Formulations containing hydrophilic (methylcellulose, carboxomer), plastic (polyvinyl chloride), and wax (glycerol palmitostearate) matrix materials incorporated with potassium chloride as active ingredient and insoluble excipients were prepared and studied in vitro using the rotating paddle method. Hardness had no markedly effect on the release characteristics of formulations except for wax matrix material formulation. Analysis of in vitro release mechanisms indicated that the most suitable results were obtained by methylcellulose and glycerol palmitostearate\textsuperscript{108}.

**Huang H. et al (1994)** evaluated an acrylic polymer-wax matrix system for oral sustained-release tablets of Diphenhydramine HCl. A desirable release profile of diphenhydramine was achieved by incorporating Eudragit L in a carnauba wax matrix. In this polymer-wax system, carnauba wax maintained the integrity of the matrix, whereas Eudragit L slowly eroded in the matrix as the drug was released. Thus, the area-to-volume ratio of the tablet remained constant over the duration of the drug release. In vitro drug release studies were conducted at physiological pH that exist in
the gastrointestinal tract. The drug release from these polymer-wax matrices is described by a combination diffusion/erosion mechanism\textsuperscript{109}.

\textbf{Dredan J. et al (1998)} focused on study was investigated the effect of the various types and amounts of polyethylene glycols on the potassium chloride release from wax matrices. Potassium chloride as a highly water-soluble model drug was embedded into wax containing surfactants to produce sustained release dosage form. Various kinds of polyethylene glycols were chosen to control the dissolution profile. The dissolution profile of the matrix samples was characterized by the Weibull distribution. On the basis of the examined physicochemical characteristics of various polyethylene glycols it is possible to select the optimal concentration of surfactant to formulate matrix dosage forms of required dissolution profile\textsuperscript{110}.

\subsection{6.2.1 Conclusion}

From the literature survey it is concluded that the different water soluble drug can be easily formulated into the sustained release formulation and release can be controlled in required passion. The matrix agent used in the formulation of hot melt technology is provide the sustained release of drug from the matrix which again aid by adding into the molten was so that the higher sustained release effect can be achieved at lower concentration of the matrix polymer.

The highly water soluble i.e. BCS class I and class III are the suitable candidate for the formulation of the sustained release tablet. Addition of the channeling agent mostly surfactant may provide suitability and assist the solubility and simultaneously controlled the dissolution rate of BCS class II and class IV low solubility drug.

The mechanism for the drug release is diffusion as well erosion occurs for the sustained drug release formulation and gives pH independent release. The direct compression method achieves better result as compare to the wet granulation method. The hardness didn’t show any marked effect in the drug release from tablet prepared by hot melt method.
6.3 Literature survey of liquisolid compact:

Gubbi S. et al (2009) reported in vitro dissolution of slightly water soluble Bromhexine hydrochloride (BXH) which could be improved by using Liquisolid system (LS). The drug release rates of LS compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of LS in increasing wetting properties and surface area of drug available for dissolution111.

Ali Nokhodchi et al (2007) investigated the potential of LS to improve the dissolution properties of a water-insoluble model drug piroxicam. The author investigated effect of physicochemical properties of piroxicam liquisolid tablets, effect of aging, and type of the carrier used. The results showed that enhanced dissolution rate of piroxicam liquisolid tablets112.

Adibkia K. et al (2014) developed new approach to formulate sustained release dosage forms of Diltiazem HCl using LS. Type of nonvolatile solvent and its physicochemical properties as well as solubility of the drug in the applied solvent found to have important role on release profile of the drug from liquisolid compacts. Amorphous form was obtained during the process of liquisolid formulation. It follows that the optimized new technique can be used to prepare sustained release formulations of water soluble drugs113.

Khalid M. et al (2010) improved the availability of Rofecoxib, a practically insoluble non-steroidal anti-inflammatory drug, as a model drug by using liquisolid technique. The effect of powder substrate composition on the flowability and compressibility of liquisolid compacts were evaluated. In addition, liquisolid tablets displayed significant enhancement of the dissolution profiles compared to commercial product114.

Naveen C. et al (2012) explore a method to improve the dissolution rate of the poorly soluble drug valsartan by delivering the drug as a liquisolid compact. The dissolution efficiency of valsartan at 15 mins was increased from 4.02% for plain drug and 13.58% for marketed product to 29.47% for the liquisolid formulation. The increase in the dissolution rate was also found to be significant compared to the marketed product at lower pH values. The liquisolid technique appears to be a promising approach for improving the dissolution of poorly soluble drugs like valsartan115.
Karmarkar A. et al (2010) evaluated sustained release liquisolid compact formulations of Tramadol hydrochloride. Two-way ANOVA results found a significant difference in dissolution profiles. This systematic approach to producing a formulation was found to help with analyzing the sustained release of Tramadol HCl. The use and evaluation of model-dependent methods is more complicated. These methods provide an acceptable model approach that indicates the true relationship between percent drug release and time variables, including statistical assumptions\textsuperscript{116}.

Mazen E. et al (2012) demonstrated that liquisolid technique is promising approach used to minimize pH dependency of dissolution rate of drug. The dissolution behavior of loratadine from liquisolid compacts was investigated in several buffered media with different pH values and it is suggested that release rates of drug from liquisolid compacts were significantly higher and less affected by pH variation compared with conventional and marketed tablets. Hence, liquisolid compacts technique used as a tool to minimize the effects of pH variation on the dissolution rate of drugs with poor water solubility\textsuperscript{117}.

Elkordy et al (2012) analyzed the effects of different liquid vehicles on release characteristics of griseofulvin as a model hydrophobic drug. Fast dissolution tablets were prepared using three different non-ionic surfactants namely Cremophor EL, Synperonic PE/L61 and Capryol TM 90, on the contrary Kollicoat SR 30D was used for formulation of griseofulvin sustained release formulations. The type of vehicles used in formulation of liquisolid compacts predict enhancement and retard the release\textsuperscript{118}.

Fahmy R. et al (2008) suggested improvement of famotidine dissolution rate through its formulation into liquisolid systems. The tested in vitro and in vivo performance of the prepared liquisolid tablets showed that all the liquisolid formulations have higher drug dissolution rates than the conventional, directly compressed tablets and having same bioavailability like the marketed famotidine tablets concerning Cmax, tmax, and AUC\textsuperscript{119}.

Spireas et al (1999) illustrated the effect of powder substrate composition on the dissolution rate of methyclothiazide liquisolid compacts. Dissolution rates were
increased by optimizing carrier-to-coating ratios in methyclothiazide liquisolid tablets containing a 5% w/w drug solution in polyethylene glycol 400 with difference excipient ratios.\textsuperscript{120}

**Leopold C. et al (2012)** examined the potential of hydrophilic aerogel formulations and liquisolid systems to improve the release of poorly soluble drugs by using griseofulvin as model drug. The commonly used carrier and coating materials in liquisolid systems Avicel and Aerosil were replaced by Neusilin, an amorphous magnesium alumino-meta-silicate to improve the liquisolid approach. Both the liquisolid compacts containing the drug dissolved in PEG 300 and the aerogel tablets showed a considerably faster drug release than the directly compressed tablets.\textsuperscript{121}

**Ali nokhadchi et al (2008)** evaluated effect of type and concentration of liquid vehicle on dissolution rate of poorly water soluble drug indomethacin from liquisolid compact. The increased rate was due to increased wetting properties of drug as well as surface of drug for dissolution.\textsuperscript{122}

**Ali Nokhodchi et al (2008)** recommended that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. Propranolol HCl tablets prepared by liquisolid technique showed greater retardation properties in comparison with conventional matrix tablets. This investigation provided evidence that Tween 80 has important role in sustaining the release of drug from liquisolid matrices, and a reduction of T\textsubscript{g} of the polymer can be the reason for the release prolongation of liquisolid tablets. The results also showed that wet granulation had remarkable impact on release rate of Propranolol HCl from liquisolid compacts, reducing the release rate of drug from liquisolid compacts.\textsuperscript{123}

**Khaled A. et al (2001)** revealed the absorption of Hydrochlorothiazide by formulating into liquisolid tablets were enhanced and proved by in vivo study using beagle dogs. There is no significant differences were observed between the two formulations with regard to the mean residence time, absorption time, and rate of absorption whereas the absolute bioavailability of the drug from the liquisolid tablets was 15% higher than that from the marketed formulation.\textsuperscript{124}
Ali Nokhodchi et al (2010) were investigated effect of liquid medication mixed with silica–Eudragit RL or RS followed by the compaction of the mixture and the effect of the type of liquid medication and HPMC concentration on drug release. Comparison study of physico-chemical properties of liquisolid tablets with conventional tablets showed that most of liquisolid formulations had superior flowability and compactibility in comparison with physical mixtures. The results suggested that the presence of non volatile co-solvent is vital to produce slow release pattern for some of liquisolid compacts. The sustained release action of HPMC was enhanced in liquisolid compacts in comparison to simple sustained release matrix tablets125.

Parmar K. et al (2014) made attempt to improve the dissolution properties of water insoluble herbal active ingredient, Embelin by utilizing liquisolid technique, which might offer improved bioavailability. The study reveals that liquisolid technique is a promising alternative for enhancing dissolution characteristics of Embelin126.

Syed I. et al (2013) suggested that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release tablets matrices of Trimetazidine Di hydrochloride water soluble drug127.

Sanka K. et al (2014) proved the potential solubility improvement strategy for efficient oral delivery of BCS class II and IV drugs. Henceforth, an attempt was made to improve the oral delivery of BCS class II drug Clonazepam (CLZ) by formulating into a novel liquisolid system. The increase in permeation of CLZ from LS formulation across rat intestine suggests the potential of formulation for improved oral delivery of CLZ128.

Elkordy et al (2014) investigated dissolution behavior of Norfloxacin as a model hydrophobic drug through application of liquisolid technology. Prepared liquisolid formulations of Norfloxacin revealed increase in the percentage of liquid vehicle does not lead to increase in the percentage of the drug release in distilled water dissolution medium129.
6.3.1 Conclusion

Liquisolid systems were originally designed to enhance dissolution of hydrophobic drugs. Recently, the same technique was explored to control drug release via hydrophobic carriers. The literature survey divulge that the liquisolid technology is used for formulation of immediate as well as sustained release formulation of highly soluble as well insoluble i.e. BCS class I and II drug. By using the liquisolid technique and formulating a liquisolid compacts the dissolution rate can be enhance or retard and there by result into the formation of immediate or sustained release formulation.

The other factors contributing in the formulation type is nature of vehicle and polymer used in the formulation. The prepared formulation of possesses the good flowability and good compactibility than conventional tablet prepared by the direct compression method. The different co-solvent can be used to increases the retardation of drug release property. The effect of matrix polymer in the liquisolid formulation showed the boosted effect than the conventional tablet formulation there by reducing the concentration of polymer simultaneously in the weight of tablet.

The fruitful effect will be observed for the herbal formulation to enhance the solubility and ultimately dissolution property. The IVIVC study showed the better absorption of drug will be takes place from the formulated liquisolid tablet than the marketed conventional tablet. Liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems.
6.4 Literature survey for HPLC method development

Shambharkar s. et al (2013) developed stability method indicating high performance liquid chromatographic method for analysis of Pazufloxacin mesylate in the presence of degradation products. The drug was subjected to stress condition of hydrolysis, oxidation, photolysis, thermal degradation. As method effectively separates the drug from their degradation products, it can be used as stability indicating method.130.


Kumar P. et al (2013) investigated stability-indicating RP-HPLC method for the determination of Rufinamide in tablet dosage forms using C18 column with mobile phase consisting of water–acetonitrile (40:60, v/v) with a flow rate of 0.8 mL/min. Rufinamide was subjected to stress conditions. The method was validated as per ICH guidelines and proves suitable for the regular analysis of drug132.

Sharma M. et al (2011) developed and validated a simple, rapid stability indicating RP-HPLC method for the determination of Repaglinide in pure and tablet forms. The method was statistically validated for accuracy, precision, linearity, ruggedness, robustness, forced degradation, solution stability and selectivity. Quantitative and recovery studies of the dosage form were also carried out. Due to simplicity, rapidity and accuracy of the method, the method is useful for routine quality control analysis133.

Auvity S. et al (2013) reported stability-indicating RP-HPLC method was developed for the determination of Betaxolol HCl. The stability-indicating capability was established by forced degradation experiments and the separation of unknown degradation products. This validated method was applied for the estimation of betaxolol hydrochloride in commercially available tablets134.

Singh L. et al (2011) reported validated, sensitive, rapid, simple and economic an isocratic HPLC method for estimating Sumatriptan succinate in tablet dosage form. System suitability tests for the assurance of quality performance of the method were performed. The method was validated for accuracy, precision, reproducibility,
specificity, and robustness, LOD and LOQ, as per ICH guidelines. The proposed method precise, accurate and reproducible, and hence can be employed for routine analysis of Sumatriptan succinate in bulk and formulations135.

Sheshla R. et al (2012) described a new, sensitive and specific isocratic RP-HPLC method with fluorescence detection was developed and validated for the determination of sumatriptan in rabbit plasma using sulpiride as an internal standard (IS). Sumatriptan was extracted from plasma by a liquid-liquid extraction. The validated method was successfully applied for pharmacokinetic study after a single oral administration of sumatriptan to rabbits136.

Jamapala B. et al (2015) revealed a simple RP-HPLC method for quantification of sumatriptan succinate in bulk and pharmaceutical dosage form. This method achieved by using isocratic elution with mixed phosphate buffer (pH: 6.8) and acetonitrile mobile phase at 70:30 ratio, with PDA detector. This method validated as per ICH guidelines. This method was simple, specific, precise, linear, accurate, robust and ruggedness for analysis of Sumatriptan succinate137.

Lavudu P. et al (2013) developed and validated a simple RP-HPLC method has been for the determination of Almotriptan malate in bulk and tablets. The method was successfully applied for the quantification of Almotriptan malate in tablets with acceptable accuracy and precision. The validated method has been successfully employed for the analysis of almotriptan malate138.

Suneetha A. et al (2010) reported an accurate, sensitive, precise and robust RP-HPLC method for the estimation of almotriptan malate in pharmaceutical dosage form Chromatographic separation was conducted C18 column at room temperature using phosphate buffer: acetonitrile (80:20) as a mobile phase, pH adjusted to 3.2 ± 0.1 with 10% sodium hydroxide, at a flow rate of 1.5 mL min⁻¹ and UV detection was performed at 227 nm. The retention time for almotriptan malate was found to be 9.47 ± 0.05 min. The method was validated stastically and applied for the quantitative analysis of almotriptan malate in bulk and formulations139.

Lavudu P. et al (2013) developed and validated a simple and rapid HPLC method for determination of the almotriptan malate in bulk and tablets. Separation was achieved using C18 column using a mobile phase consisting of chloroform, methanol and acetic
acid (80: 15: 5 v/v). An isocratic method with a flow rate of 1mL/min was used. The developed method was sensitive, precise, accurate, robust and linear over the concentration range of 1-80 µg/mL. The developed method was found to be suitable and reproducible for analysis of almotriptan malate in tablets.  


6.4.1 Conclusion

The literature revealed several methods for the estimation of almotriptan malate in bulk as well in the pharmaceutical formulation by using RP-HPLC analytical method. The developed method is validated and proves to be accurate, sensitive, rapid and simple.
6.5 Literature Survey of UV spectrophotometric method development

**Viplava Prasad U. et al (2012)** described two simple and sensitive visible spectrophotometric methods are described for the determination of almotriptan malate in bulk and pharmaceutical preparations based on the formation of colored molecular complex. The proposed methods are validated with respect to accuracy, precision, linearity and limit of detection. The suggested procedures are successfully applied to the determination of the drug in pharmaceutical preparation, with high percentage of recovery, good accuracy and precision. The results of analysis have been validated statistically by repeatability and recovery studies. The results are found satisfactory and reproducible. These methods are applied successfully for the estimation of almotriptan in tablet form without the interference of excipients.

**Suneetha A. et al (2010)** reported new simple, sensitive, precise, accurate and economical UV spectrophotometric method of analysis for almotriptan malate both as a bulk drug and in tablet formulations was developed and validated. The method employed methanol as solvent and the drug shows maximum absorbance at 227 nm. The linear regression analysis data for the calibration plot showed good linear relationship with $r^2 = 0.9999$ in the concentration range of 1–5 μg/mL. Results of analysis were validated statistically and by recovery studies.

**Ramzia I. et al (2011)** developed two spectroscopic methods were proposed for the determination of almotriptan malate (AM), eletriptan hydrobromide (EH), and rizatriptan benzoate (RB), in pure form or in their pharmaceutical dosage forms. The first method is a quantitative fluorimetric method. For Almotriptan malate induced fluorescence was measured by fluorigenic labeling with 4-chloro-7-nitrobenzofurazan (NBD-cl) upon excitation at λ 460nm, and emission at λ 550nm. The second method was based on formation of charge transfer complex between the base of the studied drugs and 7,7,8,8 tetracyanoquinodimethane (TCNQ). The colored complexes have a maximum at λ 744nm. The proposed methods were reproducible, precise and accurate and were successfully applied for the determination of each of the studied drugs in pure form or in pharmaceutical dosage form in quality control determinations.
Belal F. et al. (2014) examined highly sensitive and simple spectrofluorimetric method for the determination of Almotriptan malate and Zolmitriptan in their pharmaceutical preparations. The proposed method is based on the investigation of the fluorescence spectral behavior of the two drugs in aqueous acidic systems. The proposed method was successfully applied for the assay of commercial tablets as well as for content uniformity testing. The results were statistically compared to those obtained by comparison methods and were found to be in good agreement.