2.1 Literature review

Nirav et al\textsuperscript{1}; prepared amlodipine tablets by direct compression technique using three different superdisintegrants. sodium starch glycolate, croscarmellose sodium and crosspovidone XL-10 were used as superdisintegrants in combinations to achieve optimum release profile, disintegration time and hardness. microcrystalline cellulose was used as diluent and mannitol, mint flavor and sodium saccharin were used to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, hardness, friability, in-vitro disintegration time and drug release characteristics. The results of in-vitro disintegration time indicated that the tablets dispersed rapidly in mouth within 60 sec. Dissolution study revealed release rate of drug from the tablets was comparable with marketed tablet formulation of amlodipine besylate. The tablets had acceptable hardness of average 3 kg/cm\textsuperscript{2} and approximately 0.67\% friability. In-vitro disintegration time was reduced and in-vitro drug release was significantly improved. Hence it was concluded that using a combination of superdisintegrants viz., croscarmellose sodium and sodium starch glycolate in the ratio of 1:2 in formulation of orally disintegrating tablets of amlodipine besylate would be quite effective in providing fast onset of action without the need of water for swallowing.

Mohini et al\textsuperscript{2}; formulated fast dissolving tablet of amlodipine besylate for rapid action. Sublimation method was adapted to prepare the tablets by using a 2\textsuperscript{3} full factorial design. All formulations are evaluated for pre-compression and post-compression parameters, wetting time, water absorption ratio. The results obtained showed that the quantity of starch potato, sodium starch glycolate, camphor significantly affect response variables. The results indicated that the optimized tablet formulation provides a short DT of 8 sec with sufficient crushing strength and acceptable friability. Stability studies of optimized formulation revealed that formulation is stable.

Patil et al\textsuperscript{3}; prepared amlodipine besylate effervescent floating tablets in different formulations with polymers by employing different grades of carbopol and HPMC polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms. Formulation containing combination of HPMC K4M, HPMC K 100M and carbopol showed maximum floating time of 24 hr and gave slow and maximum drug release of amlodipine.
besylate spread over 24 hr and whereas amlodipine besylate released from marketed tablet was rapid and maximum within 12 hr.  

Roy et al\(^4\); formulated fast dissolving tablets of amlodipine besylate by direct compression technique using various concentration of super disintegrants like cross carmellose sodium (Ac-Di-Sol), polyplasdone R-XL and sodium starch glycolate (SSG). The formulated tablets were evaluated for crushing strength, friability, thickness, diameter, weight variation, drug content, wetting time, water absorption ratio, disintegration time, and percentage of drug release. All formulations showed satisfactory result. Among them formulation containing 3% of Ac-Di-Sol exhibited complete release within 12 minutes and disintegration time was within 10 sec. Dissolution data was compared with innovator for similarity factor \((f_2)\) exhibited an acceptable value >50. Accelerated stability study indicated no significant difference in assay and crushing strength. Hence, three production validation scale batches were designed based on lab scale best batch (F3) and charged for stability. All parameters were within the limit of acceptance. There was no chemical interaction between the drug and excipients during FT-IR study; considered in the present investigation.  

Chandira et al\(^5\); formulated and developed amlodipine besylate 10 mg tablets using direct compression techniques, to provide a safe, highly effective method for treating severe hypertension while reducing undesirable adverse effects. Amlodipine besylate had maximum solubility in PH3 and thus most suitable medium for amlodipine besylate dissolution studies. the dissolution profile of the formulated formulation was compared with the marketed preparation. The results indicated improved dissolution profile of formulation containing starch (4%) as a lubricating agent took 30 minutes for complete drug release.  

Sukhacvasi et al\(^6\); formulated the fast dissolving tablets of amlodipine besylate tablets using Fenugreek seed mucilagae and ocimum basilicum gum as a natural superdisintegrating agents to achieve quick onset of action, to increase the water uptake with in shortest wetting time and to decrease the disintegration time of the tablets by simple and cost effective direct compression technique. Pre-compression parameters like angle of repose and post-compression parameters like wetting time, water absorption ratio, in-vitro disintegration and in-vitro dispersion time were studied. The hardness, friability and drug content of all the formulations were found to be within the limits. The best formulations fenugreek seed mucilage (5%) & ocimum basilicum gum (5%) have shown good disintegration time (38 and 32 sec
respectively), hardness and friability. The best formulations were also found to be stable. Optimized formulation was subjected to stability studies as per ICH guidelines and it insignificant change in hardness, disintegration time and \textit{In-vitro} drug release.

Shaikh et al\textsuperscript{7}; developed a tablet formulation of S(-)-amlodipine besylate chiral separation drug and nebivolol hydrochloride for better management of hypertension. The study was also carried out to design a suitable dissolution medium for S(-) - amlodipine besylate and nebivolol drochloride. Amlodipine besylate and nebivolol hydrochloride had maximum solubility in pH 1.2 and thus pH 1.2 was selected as the most suitable media for S(-)-amlodipine besylate and nebivolol hydrochloride. The accelerated stability study of the optimized formulation was performed as the ICH guidelines. The results indicated no change in optical rotation of S(-) – amlodipine besylate. Hence, combination of two drugs can be formulated into the tablet by wet granulation technique using starch paste (5%) and MCC: stach in 60:40 ratio as filler for having satisfactory release profile in pH 1.2.

Yadav et al\textsuperscript{8}; developed a matrix-type transdermal therapeutic system containing drug amlodipine besylate with different ratios of hydrophilic (hydroxyl propyl cellulose) and hydrophobic (Eudragit RL/RS 100) polymeric systems by the solvent evaporation technique by using 30% w/w of dibutyl phthalate and PEG-400 to the polymer weight, incorporated as plasticizer. methylsulphoxide (7%) was used to enhance the transdermal permeation of amlodipine besylate. The physicochemical spectroscopy suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content and \textit{in-vitro} release rate. All prepared formulations indicated good physical stability. \textit{In-vitro} permeation studies of formulations were performed by using franz diffusion cells. The \textit{in-vitro} release of drug across rat skin results showed that the $R^2$ value of fitting model indicates that the drug release kinetics of formulations followed mixed zero-order and first order kinetics in different formulations. The formulation (HPMC E-15 and eudragit L100 in the ratio of 8:2) have showed optimum release.

Abdoh et al\textsuperscript{9}; studied the compatibility of amlodipine besylate in its solid formulations with various drug excipients. The various factors affecting amlodipine besylate stability were studied using high performance liquid chromatography (HPLC). It has been found that binary 1:1 mixtures of amlodipine besylate and an excipient are stable at 65°C and 40°C/75% RH. Further investigations were conducted
to study the stability of amlodipine besylate in multicomponent mixtures, including mixtures with actual formulations. The study revealed that mixtures of lactose, magnesium stearate, and water induce some instability on amlodipine besylate. The major degradation product confirmed by HPLC-mass spectrometry is amlodipine besylate glycosyl. This was in conformity with the well-known Maillard reaction between primary amines and lactose. Thus, lactose-free amlodipine formulations were recommended from the safety, quality, efficacy, and process cost points of view.

Dey et al.\cite{10}; developed gastro-retentive delivery system of atenolol which, after oral administration should have the ability to prolong gastric residence time with desired in-vitro release profile. Atenolol was chosen as a selective drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression technique, using natural gum such as xanthan gum and guar gum, alone or in combination. The tablets were evaluated for physical characteristics viz. hardness, friability, weight variation, content uniformity, and floating capacity. Further, tablets were evaluated for in-vitro release characteristics for 8 hr. Among all the formulations, tablets containing combination of xanthan gum and guar gum showed better floating capacity as well as sustained release of atenolol at the end of 8 hr. The mechanism of release of atenolol from the floating tablets was found to be diffusion couple with erosion. It was concluded that the tablets prepared by combination of xanthan gum and guar gum had efficient floating and sustained release capacity as compared to tablets prepared by using natural gum alone.

Khirwadkar et al.\cite{11}; studied fast dissolving tablets of atenolol using polymer like AC-DI-SOL and sodium starch glycolate which will quickly the release of drug, increasing the bioavailability of the drug and thus decreasing the dosing frequency of the drug. The description and appearance, melting point and solubility were also performed for further characterization & it was found that all results are satisfactory. And formulation containing SSG (4%) and Ac-di-sol (3%) was the best formulation among of that and it released 99.5% of drug.

Kumarte et al.\cite{12}; prepared atenolol tablets by direct compression technique using two different superdisintegrants in combination by co-process mixing and by physical mixing. Croscarmellose sodium and crospovidone were used as superdisintegrants in combinations in the different ratio (1:1, 1:2 & 1:3). The developed superdisintegrants were evaluated for angle of repose, carr’s index and hausner’s ratio in comparison with physical mixture of superdisintegrants. The angle of repose of the developed
excipients was found to be < 25°, carr’s index in the range of 10-15% and hausner’s ratio in the range of 1.11-1.14. Fast dissolving tablets of atenolol were prepared using the co-processed superdisintegrants and evaluated for pre-compression and post compression parameters. Based on in-vitro dispersion time (approximately 20sec) formulation was tested for in-vitro drug release pattern in pH 6.8 phosphate buffer and drug excipients interaction were studied with DSC. Among the designed formulations, the formulation containing 4% w/w of co-processed superdisintegrants (1:1 mixture of crospovidone and croscarmellose sodium) emerged as the overall best formulation based on drug release characteristics in pH 6.8 phosphate buffer.

Amjad et al\textsuperscript{13}; developed matrix type transdermal patches containing atenolol with different ratios of HPMC (hydroxyl propyl methyl cellulose) & EC (ethyl cellulose) by solvent casting method. Propylene glycol 3% is used as plasticizer & span 80 is used as permeation enhancer. The possible drug-polymer interactions were studied by FTIR studies. Formulated transdermal patches were evaluated with regard to physicochemical characteristics, in-vitro permeation studies and stability studies. All the prepared formulations showed good physical stability. The in-vitro permeation studies were performed using Franz diffusion cell. Out of all the formulated patches using span 80 (1%) and containing HPMC & HPMC with EC showed good permeation in 24 hrs.

Aryal et al\textsuperscript{14}; prepared multi-drug tablets of amlodipine besylate and atenolol as either mono-layer (mixed matrix) or bi-layer tablets containing each drug in a separate layer by using similar excipients and processing. Each tablet batch was packed in strip and blister packs and kept under accelerated temperature and humidity conditions. The stability of two tablet and packaging types was compared by HPLC analysis after 0, 1, 3 and 4.5 months and expressed as the content of intact amlodipine and atenolol. The content of atenolol did not decline regardless of tablet and packaging type. Amlodipine content in bi-layer tablets decreased to about 95 and 88% when packed in strips and blisters, respectively. When prepared as mono-layer tablets, the content decreased to 72 and 32%, respectively. The study revealed that the bi-layer tablet formulation was more stable than the mono-layer type. Further, the stability was increased when the tablets were packed in aluminum strips as compared to PVC blisters.

Bhowmik et al\textsuperscript{15}; developed sustained release matrix tablets of atenolol. Matrix Tablet of atenolol was designed by using different polymers viz.atarch, xanthan gum,
vee gum, guar gum, gum accacia, tragacanth, hupu gum were used as natural polymers and rudragit-L100, ethyl cellulose, sodium carboxy methyl cellulose (NaCMC), hydroxy propyl methyl cellulose (HPMC) (5&15cps), methyl cellulose, kollidon were used as synthetic polymers. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by single polymer, combination of two different rates controlling material. The FT-IR study revealed that there was no chemical interaction between drug and excipients. The granules were prepared by dry granulation method. Results indicated that granules were good flowing characteristics. After evaluation of physical properties like weight variation, hardness, thickness, friability of tablet, the different formulations checked for the percentage drug content which having good uniformity. The results of drug dissolution studies showed improved drug release, retardation effects of the polymers and could achieve better performance. After eight hr dissolution test, dissolution profiles showed that better sustained release was observed from starch and veegum containing formulation and eudragit and ethyl cellulose containing formulation of atenolol matrix tablet. It was also observed from the study that the presence of starch caused an increase in the release rate of Atenolol matrix tablet.

Varma et al\textsuperscript{16}, prepared the floating tablets of atenolol to increase the gastric retention, extend the drug release and to improve the bioavailability of the drug. The floating tablets were formulated using HPMC 100 cps, sodium alginate, carbopol 940 and guar gum as the polymers. The tablets were prepared by direct compression method. The formulated tablets were evaluated for the quality control tests: weight variation, hardness, friability, swelling index, floating lag time and total floating time. The \textit{in-vitro} release of the tablets was evaluated in 0.1N HCl (pH 1.2). The floating tablets extended the drug release up to 8 hr. The drug-polymer interaction was evaluated by fourier transform infrared spectroscopy (FTIR). The drug release from the optimized formulation followed first order kinetics (regression coefficient, \(r^2\) value =0.988) and the Higuchi equation \((R^2 = 0.996)\). The \(n\) value (0.260) calculated for the optimized formulation revealed that the drug release followed fickian diffusion. The similarity factor calculated for the batch F8 (optimized formulation) was 70.74\%, and its dissolution profile was similar to the dissolution profile of the branded extended release tablet.
Yadav et al\textsuperscript{17}; formulated and evaluated nasal drug delivery system containing salbutamol sulphate was prepared for improving the bioavailability & sustaining the drug release. Formulation was prepared using thermoreversible, bioadhesive polymers such as poloxamer and Hydroxy Propyl Methyl Cellulose (HPMC) in the form of in situ gel by cold technique. The results revealed that as the increase of bioadhesive polymer HPMC concentration, decrease in gelation temperature (T1) and increase in gel melting temperature (T2). pH of all formulation were found to be within the range between 5.5 to 6. The drug content for all formulation was found to be 96%-100%. The mucoadhesive test indicated that the level of HPMC increases, the mucoadhesive strength also increases. The developed formulations had optimum viscosity. The optimized formulation shows the controlled drug release

Narayan et al\textsuperscript{18}; formulated the salbutamol sulphate as a floating matrix tablets and control the drug release up to 24 hr for administration as once daily dose. Salbutamol sulphate is a short acting bronchodilators which have short biological half life about 2-4 hr. Floating matrix tablets were formulated by using swelling polymer like ethylcellulose, Hydroxy propyl methyl cellulose (K100M, K4M) with different concentration 25, 50, 75 % w/w of the polymer were used for the preparation of the floating matrix tablets. The formulation variables like hardness, polymer concentrations, and shape of the tablets were optimized to achieve the floating nature of the tablet in stomach for 24 hr. In addition stearic acid was included in this formulation to evaluate their release characteristics. From this the hydrophilic floating matrix control the release up to 12 hr with HPMC K100M at 75% w/w of the polymer concentration. The formulations, which had stearic acid retards the drug release by controlling the water penetrations in to the floating matrix tablets, sustained their drug release above 12 hr. The floating matrix tablets with minimum hardness of 5 kg/cm\textsuperscript{2} and round shaped tablets exhibited better buoyancy.

Sahu et al\textsuperscript{19}; developed floating matrix tablets of salbutamol sulphate using ethyl cellulose and acrycoat S-100 as polymers, and sodium bicarbonate, citric acid and tartaric acid as gas generating agents. The floating tablets were prepared by wet granulation technique, and the granules were compressed at a pressure of 5.0 kg/cm\textsuperscript{2}. The tablets contained drug, ethyl cellulose and acrycoat S-100 (as release retarding polymers), sodium bicarbonate, citric acid and tartaric acid (as gas formers) as well as various additives. The tablets were made by wet granulation technique. The formulations were evaluated for \textit{in-vitro} buoyancy, dissolution and \textit{in-vitro} drug
release. All the formulations fulfilled the essential requirements for good floating systems. Formulation containing citric acid and sodium bicarbonate, showed lower lag time and longer floating duration than the formulations containing only sodium bicarbonate. Formulation containing citric and tartaric acid at a ratio of (1:1) showed longer floating duration (9 hr). As the concentration of sodium bicarbonate increased in formulation, drug release decreased while floating duration increased. It was concluded that from all the 24 formulations, the one containing tartaric acid and citric acid in ratio 1:3 and 12 mg sodium bicarbonate showed the highest floating duration and least lag time.

Dineshmohan et al\textsuperscript{20}; prepared salbutamol sulphate tablets by direct compression method using superdisintegrants such as primojel, kollidon CL, L-Hydroxy propyl cellulose. The prepared tablets were evaluated for weight variation, thickness, friability, hardness, drug content, \textit{in-vitro} disintegration and \textit{in-vitro} drug release. From characterization of fast dissolving tablets of salbutamol sulphate, it was concluded that formulation containing kollidon CL is most acceptable. The fast dissolving tablet of salbutamol sulphate 4\% w/w and kollidon CL as the superdisintegrant is an alternative to and better than the conventional tablet dosage form used in the management of asthma.

Shah et al\textsuperscript{21}; developed formula based on pulsatile delivery of salbutamol sulphate which can offer a solution for exhibiting chronopharmacological behavior of asthma, extensive first-pass metabolism and necessity of night-time dosing. It was concluded among five batches specific amount 4\% CAP and 2\% EC batch gives late release than predetermined time. They release their higher dose after 6 hr. So that formulation was accurate for nocturnal asthma according to pulsatile drug delivery system.

Yilma et al\textsuperscript{22}; formulated and optimized a sustained release floating tablet of salbutamol sulphate using xanthan gum (XG) and HPMC as release retarding agents and NaHCO3 as floating aid to improve its bioavailability and reduce its dosing frequency. Floating tablets were prepared by wet granulation technique and drug release analysis was done using PLC. The effects of percentage of polymer, polymer type (XG or HPMC), polymer ratio XG/HPMC; (1:1, 1:3, 3:1) and percentage of NaHCO3 on floating lag time, floating duration, cumulative release within 1 h, and release rate were investigated. In conclusion, this study had come up with an optimum formula for the development of floating tablet of salbutamol sulphate that could
remain buoyant and release the drug over a period of 12 hr in a sustained manner *in-vitro*.

**Malodia et al**\(^{23}\); formulated and evaluated salbutamol sulphate matrix tablets, extended release dosage form, for the treatment of Chronic Obstructive Pulmonary Disease (COPD). The ER tablets were prepared by direct compression method using two polymers such as hydroxyl propyl methyl cellulose (HPMC K100M) and xanthan gum in varying ratios. Powder blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content. The results of all these tests were found to be satisfactory. The *in-vitro* dissolution study was carried out for 24 hr using type II dissolution apparatus. Formulation containing 20% HPMC and 30% xanthan Gum showed 96.49% of drug release at the end of 12 hr. This finding revealed that above a particular concentration of HPMC K-100M and xanthan gum were capable of providing extended drug release.

**Khan et al**\(^{24}\); prepared gastro retentive floating tablets of theophylline. Hydrophilic polymer methosel K4M was used for its gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agent (methocel K4M) and dose variation on drug release profile and floating properties were investigated. It was observed that in all cases increase of the amount of floating agent caused a decrease of the floating lag time. Increase of theophylline load showed an increase of the floating lag time, which was independent of floating agent content. The release mechanisms were explored and explained with zero order, first order, Higuchi, Korsmeyer and Hixon-Crowell equations. The release rate, extent and mechanisms were found to be governed by the content of polymer and floating agent. The content of active ingredient was also a vital factor in controlling drug release pattern. It was found that polymer content and amount of floating agent significantly affected the time required for 50% of drug release (T\(_{50}\)), percentage drug release after 8 hr, release rate constant, and diffusion exponent (\(n\)). Kinetic modeling of dissolution profiles revealed that the drug release mechanism could range from diffusion controlled to case II transport, which was mainly dependent on presence of relative amount of theophylline, polymer and floating agent.
Bijumol et al\textsuperscript{25}; formulated oral gastro retentive floating tablets of theophylline was using gel-forming hydrophilic polymers, HPMCK4M, HPMCK100M and HPMC 15cps. The work also focused on \textit{in-vivo} evaluation of buoyancy by x-ray imaging. Suitable \textit{In-vitro} methods for estimating the drug release from the tablet as a function of time were developed and compared with marketed product (TheoSR200mg). The prepared tablets exhibited satisfactory physicochemical characteristics. All the prepared batches showed good \textit{in-vitro} buoyancy. The tablets with HPMCK4M and HPMCK100M floated for longer duration and had more matrix integrity as compared to formulations containing HPMC 15cps. Formulations with HPMCK100M & HPMCK4M showed better control of drug release and the drug release was similar to that of marketed product.

Sadafal et al\textsuperscript{26}; developed and evaluated an oral pulsatile drug delivery system to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 6 hr (± 0.25 h). The basic design of the system consisted of a rapid release tableted core and a controlled release tableted coat. A combination of isopropyl alcohol (70\%) and acetone (30\%) was used as solvent for eudragit S100 coating. An \textit{in-vitro} dissolution study of the prepared tablet was conducted initially for 2 hr in simulated gastric fluid and after that medium was changed to intestinal fluid pH 7.4.

Kouchak et al\textsuperscript{27}; prepared floating system using the emulsification-solvent diffusion method to prolong the gastric emptying time of theophylline. Theophylline, ethyl cellulose and dibutyl phthalate were dissolved in an ethanol/dichloromethane mixture, added to 0.1 M HCl containing NaCl (20\%) or saturated theophylline and/or different concentrations of polysorbate 80 and polyvinyl alcohol. The mixture was stirred at different speeds for 3 hr. The resulting microspheres were separated from the solution by filtration. Physical characteristics, including the shape and size distribution, floating capability, drug loading and drug release of the resulting theophylline microspheres were investigated. The prepared microspheres tended to float over the simulated gastric medium for over 12 hr. Addition of NaCl (20\%) to the aqueous phase increased the drug loading of microballoons. The mean geometric diameter of microspheres decreased, as the stirring speed rate or the polysorbate 80 concentration were increased. Microballoons prepared at higher stirring rates released their drug content faster. It was concluded that particle size and floating capability of
microballoons could be adjusted by altering the stirring rate during microencapsulation.

Chaudhary et al.\textsuperscript{28}, described the influence of the high substituted hydroxypropyl cellulose (HPC-H) and guar gum on release behavior and kinetics of theophylline sustained release tablets using $3^2$ full factorial designs. The amounts of guar gum ($X_1$) and HPC-H ($X_2$) were selected as an independent variables and drug release at 1hr ($Q_1$) and at 8hr ($Q_8$) and time required for 50\% drug release ($T_{50\%}$) were selected as a dependent variable. Theophylline tablets were prepared by direct compression method using HPC-H with guar gum as release retardant in different proportions and MCC as directly compressible filler-binder. The parameter optimized using $3^2$ factorial designs and evaluated for various evaluation parameters. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Regression analysis and response surface analysis were performed for dependent variables. The FTIR study was carried out for drug excipient compatibility Studies. The initial release was sufficiently higher in all formulations thus ruling out the need to incorporate a specific loading dose. Thus, the use of suitable polymer combinations that could provide initial higher release and release extension up to 12 hr. It was observed that type and ratio of polymer had significant influence on $Q_8$, without significant influence on $Q_1$ and $T_{50\%}$. Mathematical treatment of the \textit{in-vitro} drug release data suggests that, the drug release of all the formulations followed Korsmeyer-peppas model, the release exponent $n<0.5$ indicate that drug diffused through the polymeric matrix by a fickian (case I) diffusion mechanism.

Bindu et al.\textsuperscript{29}; reviewed bi-layer tablet which was a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. General tablet manufacturing principles remain the same, there is much more to consider because
making multi-layer tablets involves multiple often incompatible products, additional equipment and many formulation and operation challenges. The present article provides an introduction to bi-layer tablet technology, challenges in bi-layer tablet manufacturing, various tablet presses used, quality and GMP requirements for their production various techniques used for bi-layer tabletting and recent developments in the field of bi-layer technology.

Jayprakash et al\(^{30}\); formulated bilayer tablets of amlodipine besilate (IR) and metoprolol succinate (SR) for the management of hypertension. In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and was directly compressed. For sustained release portion HPMC polymers were used in granulation stage and also extragranularly. The compressed bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and invitro drug release using USP dissolution apparatus type 2 (paddle). Result showed 9.96%, 35.56%, 52.12%, 90.46% release for metoprolol succinate in 1, 4, 8, 20 hr respectively. However, Amlodipine besilate released 98.28% at the end of 30 minutes. The IR spectrum and DSC studies revealed that there was no disturbance in the principal peaks of pure drugs metoprolol succinate and amlodipine besilate. The stability studies were carried out for the optimized batch for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

Toma et al\(^{31}\); formulated aspirin and clopidogrel together as floating bilayer tablet system. Three different formulas of 75 mg aspirin were prepared by wet granulation method as immediate release layer; different disintegrants used to achieve rapid disintegration. Formula with crosscarmellose as disintegrant achieve rapid disintegration was selected for preparation of bilayer tablet. Different formulas of 75 mg clopidogrel were prepared as sustained release floating layer by wet granulation (effervescent) method; the physical and floating properties for compressed clopidogrel matrix were studied in addition to study the effect of polymer concentration(HPMC), and its combination with ethyl cellulose and carbopol, effect of different diluents and effect of increasing sodium bicarbonate amount on the release from compressed matrix. Formula prepared with HPMC and EC in a ratio of 1:1 was capable to retard the release of clopidogrel for 6 hr in addition to its good floating behavior and therefore selected to prepare bilayer tablets in combination with
selected aspirin layer. The prepared bilayer tablets were further subjected to
evaluation of their physical, floating properties and release behavior. Finally the
kinetic study reflects acceptable shelf life for aspirin and clopidogrel.

**Wolfram Eisenreich**\(^{32}\); patented bilayer tablet which comprises a first layer
formulated for instant release of the angiotensin II receptor antagonist telmisartan
from a dissolving tablet matrix and a second layer formulated for instant release of the
calcium channel blocker amlodipine from a disintegrating or eroding tablet matrix.

**Kulkarni et al**\(^{33}\); prepared bilayer floating tablets of lovastatin and atenolol
comprised two layers, i.e immediate release and controlled release layers. The
immediate release layer comprised sodium starch glycglycollate as a super disintegrant
and the sustained release layer comprised HPMC K100M and xanthan gum as the
release retarding polymers. Sodium bicarbonate was used as a gas generating agent.
Direct compression method was used for formulation of the bilayer tablets.
Accelerated stability studies were carried out on the prepared tablets inaccordance
with ICH guidelines. Roentgenography was carried out to study the *in-vivo* buoyancy
of the optimized formulation. All formulations floated for more than 12 hr. More than
90% of lovastatin was released within 30 min. HPMC K100M and xanthan gum
sustained retarded the release of atenolol from the controlled release layer for 12 hr.
After stability tests, degradation of both drugs were found but the drugs, contents
were found to be within the range. Diffusion exponents (*n*) were determined for all
the formulations (0.53-0.59). The release of atenolol was found to follow a mixed
pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The
optimized formulation was found to be buoyant for 8 hr in stomach.

**Solanki et al**\(^{34}\); developed a bilayer floating tablets of valsartan to increase the
bioavailability of valsartan by increasing dissolution and give sustained release action
up to 24hrs by single unit dosage. Valsartan:β-cyclodextrin complex was prepared by
kneading method. Bilayer floating tablets of valsartan its inclusion complex with β-
cyclodextrin (βCD) were formulated by direct compression method. The immediate
release layer comprised of sodium starch glychlorlate as a super disintegrate and
sustained release layer comprised of ethyl cellulose and HPMC K100M as release
retarding polymers to control the drug release and restrict the region of drug release to
stomach. A \(3^2\) factorial design was applied to optimize the drug release profile. A 5.3
fold increase in the dissolution efficiency of valsartan was observed with
valsartan:βCD in the ratio of 1:1. Trial batches of IR layer tablet shows best result
with SSG 6%. After application of factorial design it was found that formulation F6 (30% HPMC K100M & 6% ethyl cellulose) release 98.44% of valsartan in 24 hr with desired floating lag time (236 sec.) and constantly floated on dissolution medium for up to 24 hrs. From the study it was concluded that a sustained release bilayer dosage form of valsartan for 24 hr can be formulated using dissolution enhancement approach.

**Dineshkumar et al**\textsuperscript{35}; prepared a bilayer tablet which contains an immediate release portion and a floating layer. HPMC-K-100, HPMC-K-4M, HPMC-E-15, carbopol-934 were used as gel forming agents either alone or in combination. Sodium bicarbonate, and citric acid as gas generating agent, lactose as additive combine with the polymer to form the floating layer. The bilayer tablets were characterized by lag time, floating time, weight variation, drug content and dissolution profile. Best Formulation [HPMC-K100 (1:1)] shows lag time of 25 sec, floating time of 24 hr and drug release of 99.85%. The best formulation was taken up for animal studies as approved by Institutional Animal Ethical Committee. The X-ray studies for floating properties of tablet and the *in-vivo* bioavailability studies for the formulation was carried out using rabbits which showed a significant increase in bioavailability of drug as compared with conventional dosage forms. The optimized formulation was subjected to stability studies at 40 ± 2°C and 75 ± 5% RH for period of three months. Short term stability studies were carried for optimized formulation showed good result.

**Solanki et al**\textsuperscript{36}; developed a bilayer floating drug delivery system that contains two layers immediate release layer and sustain release layer. First immediate release layer quickly released drugs and attains onset of action, subsequently floating sustained release layer floated over gastric fluid and released the drug in sustained or controlled manner. Immediate release layer contained repaglinide, sodium starch glycolate & microcrystalline cellulose. In this study floating sustain release layer tablets were prepared using HPMC K4M alone, Na CMC alone & combination of HPMC K4M & Na CMC. Sodium bicarbonate & citric acid were used as an effervescent agent. All formulations were prepared by using factorial design (3\textsuperscript{2} & 2\textsuperscript{3}). All the above formulations were evaluated for *in-vitro* drug release, buoyancy lag time (BLT), swelling ability and floating behavior. All formulations showed anomalous transport mechanism. Finally bilayer floating sustained release tablets was formulated by using optimized immediate release layer and optimized floating sustained release layer &
evaluated as earlier. The optimized bilayer tablet formulation was subjected to stability study 40°C±2°C/75%RH±5%RH for 1 month according to ICH guidelines & evaluated. It was concluded that by this method the formulation containing 8% SSG and 10% HPMC K4M was the best and can be successfully developed novel bilayer floating tablet which exhibit a unique combination of floatation for prolonged residence in the stomach by attaining quick onset of action.

**Karen et al**\(^37\); formulated floating tablets of itopride hydrochloride using an effervescent approach for gastroretentive drug delivery system designed to prolong the gastric residence time and thereby increase drug bioavailability, and drug release rate using direct compression method; containing Itopride hydrochloride, polymers HPMC K100M, HPMC K15M and HPMC K4M, along with gas generating agent sodium bicarbonate. The floating tablet formulations were evaluated for physical characterization, assay, swelling index, in-vitro drug release, hardness, friability and weight variation. From the characterization of the formulation, it was concluded that the drug release from the matrix tablet was slow and spread over 24 hr. Among three grades of HPMC polymer HPMC K100M is suitable for design of once a daily sustained release formulation of itopride hydrochloride.

**Sandeep et al**\(^38\); reviewed that among all dosage forms tablet was the most popular dosage form existing today because of its convenience of self administration, compactness and easy manufacturing; sometimes immediate onset of action was required than conventional therapy in many cases. For overcoming these drawbacks, immediate release dosage form had emerged as alternative oral dosage forms. Immediate drug release dosage forms disintegrated rapidly after administration with enhanced rate of dissolution. The basic approach used in development tablets was the use of superdisintegrants like cross linked polyvinylpyrrolidone or crospovidone (Polyplasdone), sodium starch glycolate (Primogel, Explotab), carboxymethylcellulose (Croscarmellose) etc. These superdisintegrants provide instantaneous disintegration of tablet after administration in stomach. In this field immediate release liquid dosage forms and parenteral dosage form had also been introduced for treating patients. In liquid dosage form can be suspensions with typical dispersion agents like hydroxypropyl methylcellulose, AOT (dioctylsulfosuccinate) etc. The development of immediate release therapy also provided an opportunity for a line extension in the marketplace, a wide range of drugs e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines and other drugs could be considered
candidates for this dosage form. As a drug entity nears the end of its patent life, it was common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allowed a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen.

Islam et al\textsuperscript{39}; designed acetaminophen extended release bi layer tablets containing immediate release layer and extended release layer. Tablets were prepared by wet granulation technique using different grades of hydroxypropylmethyl cellulose (HPMC 15 cps, HPMC 100 cps and Methocel K4M ) as release rate retardant and tablets were evaluated for hardness, friability, weight variation, thickness and drug content uniformity. \textit{In-vitro} release studies were performed using USP type II apparatus (paddle method) in 900 mL of 0.1N HCl at 50 rpm for 4 hr and compared with USP specification. \textit{In-vitro} release studies revealed that the release rate decreased with increase of polymer loading and viscosity. Formulation containing 10\% HPMC 100 cps and 1.5\% sodium starch glycolate and containing 1.5\% methocel K4M CR and 0.5\% sodium starch glycolate were found to follow compendia specification for drug release profile. Drug release was analyzed using zero-order, first order, Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the bi layer matrix tablets. Mathematical analysis of the release kinetics indicated that release from the matrix tablets followed fickian diffusion. So the bi-layer tablets could be a potential dosage form for delivering acetaminophen

Mali et al\textsuperscript{40}; developed the simultaneous estimation of atenolol and amlodipine besylate in bulk and combined tablet dosage form. They developed two methods; the first method was based upon the simultaneous equation and second upon the determination of Q value. Atenolol and amlodipine had absorption maxima at 224.4 and 238.2 nm respectively. Beer’s law obeyed in concentration range of 2-24 μg/mL and 2-34 μg/mL for ATN and AMN respectively. The method of Q analysis was based on measurement of absorptivity at 224.4 nm and at isorptive point 232.2 nm. The recovery studies from tablet were indicative of accuracy of method and were found in between 99.87-101.43\% at three different levels of standard additions. Precision studies showed satisfactory results. A novel approach to use 0.02\% SLS as
solvent was proved to be beneficial with respect to cost, stability and avoidance of organic solvent. 

**Pawar et al**⁴¹; developed the simultaneous estimation method of atenolol and amlodipine besylate. Spectroscopic studies were carried out using double beam U.V.Spectrophotometer model JASCO. The marketed combination of atenolol and amlodipine besylate that is Primol-AT 10 TAB Madley pharma and 0.1N HCl used as solvent. Then spectra of AML and ATN exhibit λmax of 239nm and 228nm respectively. Addionaly one isosorpptive point was observed at 233nm this wavelength were selected for simultaneous estimation of AML and ATN and standard Calibration curves for AML and ATN were linear with correlation coefficient 0.996 and 0.993 at all selected wavelengths. This method was found to be applicable over a range of 4-24ug/mL for AML and ATN. This method can be used as alternative for rapid and routine determination of bulk sample and tablets.

**Mishra et al**⁴²; developed a simple, sensitive and specific UV spectrophotometric method for the estimation of salbutamol in tablet dosage form. The optimum conditions for the analysis of the drug were established. The wavelength maxima (λmax) for salbutamol were found to be 276 nm. The linearity for this method was found to be in the range of 10-120μg/ml. The method showed high sensitivity with reproducibility in results. The lower limit of detection and the limit of quantification were found to be 4.234 and 12.702 respectively. The calibration curve was drawn by plotting graph between absorbance and concentration. Coefficient of correlation was higher than 0.99. The regression of the curve was Y = 0.002x + 0.0821. Precision of the method was found to be 1.625 ± 0.324 against the label claim of 4mg. The percentage recovery was found to be 98.56±0.238. The sample solution was stable up to 12 hr. They concluded that the proposed method might be suitably applied for the analysis of salbutamol in tablet pharmaceutical formulation for routine analysis.

**Manasa A**⁴³; described two simple spectrophotometric methods (UV and Visible) for the assay of salbutamol in bulk form and in pharmaceutical formulations. Method A was based on UV method where water was used as solvent and the drug was dissolved in it and measure at a λmax of 273nm. Method B was based on the reaction of salbutamol with sodium carbonate, hydroxyl ammonium chloride to form a green color chromogen with λmax at 701nm.

**Maha Kadhim S**⁴⁴; developed a new simple and sensitive colorimetric method for determination of salbutamol in aqueous solutions. The method was based on the
formation of a yellow colored azo dye by diazotization of 2, 4-dichloroaniline, followed by a azo-coupling reaction between the resulting product and salbutamol. The maximum absorbance of azo dye at 447 nm. Beer's law was found to be obeyed in the concentration range of 2.5-20 μg/mL with range of molar absorptivity between (4000-7265) Lmol⁻¹cm⁻¹. The optimum reaction conditions and other analytical parameters were evaluated.

2.2 References


