2. LITERATURE REVIEW.

Sonia Pandey et al., (2010), formulated Carvedilol bilayered buccal tablet in order to avoid the first-pass effect and decrease the drug loss using different polymers and excipients. Eight formulations were made using different ratio of carbopol 934P and HPMC K4M. The formulations were tested for in vitro drug release, in vitro bioadhesion, moisture absorption and in vitro drug permeation through porcine buccal mucosa. The dissolution of Carvedilol from all the prepared tablets into phosphate buffer (pH 6.8) was controlled and followed by non-fickian release mechanism. Dissolution studies of the tablets of optimized batch containing 5% Carbopol 934P/65% HPMC K4M/30% lactose showed 82.7% release of drug in 6 hrs.

P. Dinesh Kumar, et al., (2010), prepared bilayer gastro retentive tablet of ranitidine using direct compression technology and optimize the type and concentration of polymer to give maximum retentive effect with good drug release profile. Ranitidine H$_2$ receptor antagonist having short biological half life (2-3.5 h), absorption in the initial part of the small intestine and 50% absolute bioavailability of drug favor development of sustained release floating formulation. In this study, a bilayer tablet was prepared 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 BLF6 [HPMC-K100 (1:1)] shows lag time of 25 s, floating time of 24 h and drug release of 99.85%.

R. Nagaraju. et al., (2009), Formulated & Evaluated bilayere tablet of salbutamol & Theophyline. The combination of these two drugs in a single dosage form will enhance the patient compliance and prolong bronchodilation. Various polymers, such as hydroxy propyl methylcellulose K4M (HPMC- K4M), hydroxy propyl methylcellulose K100M (HPMC-K100M), xanthan gum, ethyl cellulose and hydroxy propyl methylcellulose phthalate (HPMC-P) were studied. HPMC-P and HPMC- K4M were found to be best in controlling the release. In-vitro dissolution studies were carried out for all the bi-layered tablets developed using USP dissolution apparatus type 2 (paddle). It was found that the tablet FB15-FW3 showed 50%
release of salbutamol in first hour and the remaining was released for eight hours. However, theophylline was found to be released as per the USP specifications.

**Atram SC et al., (2009)**, Developed and optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by optimization technique. A 32 factorial design was employed in formulating bilayer tablet with individual release layer i.e. sustained release layer and immediate release layer. The independent variables selected both cases HPMC(X1), Starch 1500 (X2) and SSG (X1), MCC (X2), respectively. Two dependent variables were considered: t50 (Y1), Q12 (Y2) and t50 (Y1), Q2 (Y2), respectively. The main effect and interaction terms were quantitatively evaluated using mathematical model. Bilayer tablets were evaluated for thickness, hardness, friability, drug content and in vitro dissolution studies.

**Ajit Kulkarni et al., (2009)**, Prepared bilayer regioselective floating tablets of atenolol and lovastatin to give immediate release of lovastatin and sustained release of atenolol. Bilayer floating tablets comprised two layers, i.e immediate release and controlled release layers. The immediate release layer comprised sodium starch glycollate 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 in accordance with ICH guidelines. Roentgenography was carried out to study the in vivo buoyancy of the optimized formulation. All formulations floated for more than 12 h. 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 h. After stability tests, degradation of both drugs were found but the drugs, contents were found to be within the range.

**Bhavesh Shiyani, et al., (2008)**, prepared bi-layer tablet of Metoclopramide Hydrochloride (MTH) and Ibuprofen (IB) for the effective treatment of migraine. MTH and IB were formulated as immediate and sustained release layer respectively. MTH was formulated as immediate release layer by using various disintegrants like Ac-Di-Sol, Polyplasdone XL, Explotab, Agar
and Gellan Gum. Treated form of gellan gum and agar was prepared and compared for their disintegrant efficiency with other disintegrants. IB was formulated as sustained release layer using hydrophilic matrix (hydroxypropylmethylcellulose [HPMC K4M]). The effect of concentration of hydrophilic matrix (HPMC K4M), binder (polyvinylpyrrolidone [PVP K30]) and buffer (sodium bicarbonate) on IB release was studied. The dissolution study of sustained release layer showed that an increasing amount of HPMC or PVP K30 results in reduced IB release. The inclusion of buffer (sodium bicarbonate) enhanced the release of IB from sustained release layer. The rational for formulation of bi-layer tablet of these two drugs in combination was MTH increases the absorption of acidic non-steroidal anti-inflammatory drug (NSAID) by increasing gastric motility. MTH was degraded when prolonged contact with acidic NSAID. Bilayer tablet was suitable for preventing direct contact of these two drugs and thus to maximize the efficacy of combination of two drugs for migraine.

**Chinam Niranjan Patra, et al., (2007),** Developed bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, eudragit RLPO and eudragit RSPO for the sustaining layer. *in vitro* dissolution studies were carried out in a USP 24 apparatus i.e. the formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. *in vitro* dissolution kinetics followed the higuchi model via a non-fickian diffusion controlled release mechanism after the initial burst release.

**Vishnu M. Patel, et al., (2007),** Formulated mucoadhesive bilayer buccal tablets of propranolol hydrochloride using the bioadhesive polymers sodium alginate (Na-alginate) and Carbopol 934P (CP) along with ethyl cellulose as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release, ex vivo drug permeation, ex vivo mucoadhesion, and in vivo pharmacodynamics in rabbits. Tablets containing, Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of in vitro drug release without disintegration in 12 hours. The swelling index was proportional to Na-alginate content and inversely proportional to CP content. The surface pH of all tablets was found to be satisfactory (7.0 ± 1.5), close to neutral pH; hence,
buccal cavity irritation should not occur with these tablets. The mechanism of drug release was found to be non-Fickian diffusion and followed zero-order kinetics.

Ziyaur rahman et al., (2006), Developed a bilayer-floating tablet (BFT) of captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior and *in vitro* dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 24 h *in vitro*, while the floating lag time was 10 min and the tablet remained floatable throughout all studies.

C. Narendra, et al., (2006), Developed and optimized gastric floating drug delivery system (GFDDS) containing metoprolol tartrate (MT) as a model drug by the optimization technique. A $2^3$ factorial design was employed in formulating the GFDDS with total polymer content-to-drug ratio ($X_1$), polymer-to-polymer ratio ($X_2$), and different viscosity grades of hydroxypropyl methyl cellulose (HPMC) ($X_3$) as independent variables. Four dependent variables were considered: percentage of MT release at 8 hours, $T_{50\%}$, diffusion coefficient, and floating time. The main effect and interaction terms were quantitatively evaluated using a mathematical model. The results indicate that $X_1$ and $X_2$ significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was nonsignificant. Regression analysis and numerical optimization were performed to identify the best formulation. Fickian release transport was confirmed as the release mechanism from the optimized formulation. The predicted values agreed well with the experimental values, and the results demonstrate the feasibility of the model in the development of GFDDS.

F. Podczeck et al.,(2006), studied the tensile strength of model materials (dicalcium phosphate dihydrate, microcrystalline cellulose and pregelatinised starch) compacted to form tablets in the form of beams consisting of two layers of equal thickness has been determined by three-point loading. The values of the tensile strength of the materials were sometimes higher and sometimes lower than the tensile strength of beams of the same thickness composed of a single material. Correction of the values for the tensile strength of the layered beams for the differences in the
elasticity of the materials in the layered tablets failed to correct for these differences, as did considering the layered beams as beams of half thickness. For a layered tablet with pregelatinised starch at the bottom and microcrystalline cellulose at the top, the value of the tensile strength recorded appeared to be that of the microcrystalline cellulose as the fracture propagated across the boundary between the layers and into microcrystalline cellulose. What appeared to be the important factor was the way the failure of the beam crossed the interface between the two layers.

Subas C. Dinda et al., (2011), studied to formulate a fixed dose combined drug formulation of valsartan (VAL) as an immediate release layer and metformin HCl (MHCl) as a sustained release form using bilayer tablet technology, which enables biphasic drug release for once daily dosing to get a better therapeutic efficacy. The immediate release layer was prepared using super disintegrant crospovidone and extended release layer using hydroxypropylmethylcellulose (HPMC K100M), sodium carboxy methyl cellulose and povidone K90. The physicochemical compatibility and stability of the tablets were determined by Fourier transform infrared spectroscopy (FTIR), X-ray diffractometry (XRD) and differential scanning calorimetry (DSC). Bilayer tablets were subjected to accelerated stability studies for 6 months. The in-vitro release studies indicate that bi-layer tablets effectively control the drug release. Bilayer tablets were evaluated for hardness, friability, weight variation, thickness, and drug content uniformity and subjected to in vitro drug release studies using different kinetic models. The amount of VAL and MHCl released at different time intervals were estimated by HPLC method. FTIR, XRD and DSC data for the formulations indicate good compatibility and stability. These tablets exhibit no significant change either in physical appearance or dissolution pattern after storage at accelerated condition (40±2°C / 75±5%RH) for 6 months. The results indicated that VAL and MHCl could be a potential fixed dose combination form for the simultaneous treatment of hypertension and diabetes and can be developed into suitable bilayer tablets.

Chuan-Yu Wu; et al., (2009), Developed Bi-layer tablets to achieve controlled delivery of different drugs with pre-defined release profiles. However, the production of such tablets has been facing great difficulties as the layered tablets are prone to fracture. In this paper, the compaction behaviour of binary mixtures and bilayer tablets of two common pharmaceutical excipients, Microcrystalline cellulose and lactose, is investigated. The effects of compositions
and compaction pressure on the compaction behaviour of binary matrix mixtures and bilayer tablets are also explored. The delamination phenomena during the manufacturing of bilayer tablets and fracture patterns of tablets subjected to diametrical compression are examined using X-ray computed tomography. The mechanical properties of binary and bilayer tablets of the same composition were also determined and compared. It has been shown that for binary and bilayer tablets with the same composition, the apparent crush strength of these binary and bilayer tablets measured from diametrical compression tests were generally comparable for the powders considered in this study. It was also found that, using the same compaction process, the relative densities of the tablets were generally different when different compositions were used, especially when the maximum compression pressure is relatively low.

Anil Chaudhary et al., (2011), Formulated Microporous bilayer osmotic tablet bearing dicyclomine hydrochloride and diclofenac potassium was developed using a new oral drug delivery system for colon targeting. The tablets were coated with microporous semipermeable membrane and enteric polymer using conventional pan-coating process. The developed microporous bilayer osmotic pump tablet (OPT) did not require laser drilling to form the drug delivery orifice. The colon-specific biodegradation of pectin could form in situ delivery pores for drug release. The effect of formulation variables like inclusion of osmogen, amount of HPMC and NaCMC in core, amount of pore former in semipermeable membrane was studied. Scanning electron microscopic photographs showed formation of in situ delivery pores after predetermined time of coming in contact with dissolution medium. The number of pores was dependent on the amount of the pore former in the semipermeable membrane. In vitro dissolution results indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 24 h. The developed tablets could be effectively used for colon-specific drug delivery to treat IBS.

Fridrun Podczeck et al., (2010), Determined the tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. While these grades are chemically identical, they differ significantly in their particle size distribution and in their mechanical properties such as Young’s modulus of elasticity. Tablets were produced in the shape of beams of similar dimensions using uniaxial compression, and solid beams made from one material only were compared with bilayered beams made from various combinations of powders. It was found that in
the production of layered tablets it is important for the purpose of quality assurance and control that the upper and lower layer of the compact can be identified. Otherwise, tensile strength measurements will result in large variability depending on which layer faces upwards during the test. Both particle size and Young’s modulus of elasticity influenced the overall strength of layered tablets. If the material forming the lower layer was more elastic, then the beam strength was reduced due to tension introduced into the system, acting especially at the layer interface and potentially causing partial or complete delamination. Larger differences in the particle size of the materials forming the tablet layers resulted in an overall reduced compact tensile strength.

**B. Vijaya Kumar et al. (2010)**, Developed Bilayer tablet of guaifenesin (GBT) using superdisintegrant MCC and sodium starch glycolate for the fast release layer and metalose 90 SH and carbopol 934 for the sustaining layer. The guaifenesin SR granules of different formulation were evaluated for bulk density, tapped density, angle of repose, Carr’s index and Hausners ratio and results were found to be 0.460 ± 0.12 to 0.515 ± 0.03 gm/cm³, 0.550 ±0.03 to 0.590 ±0.04 gm/cm³, 19 ±0.01 to 26 ± 0.23, 13.72 ± 0.03 to 19.56 ± 0.04 & 1.137 to 1.196, respectively. The prepared bilayer tablets were evaluated for weight variation, hardness, friability, drug content and *in vitro* drug release. *In vitro* dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. *In vitro* dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release. Stability studies conducted for optimized formulation did not show any change in physical appearance, drug content, matrix integrity and in vitro drug release. The results of the present study clearly indicated that GBT was a stable dosage form and a promising potential of the guaifenesin bilayer system as an alternative to the conventional dosage forms.

**Girish S. Sonar et al., (2007)**, Developed bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach using rosiglitazone maleate as a model drug. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single
station rotary press. Granules and tablets were characterized using the official method. Hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer and, when immersed in 0.1 mol/l HCl, the tablet expands and rises to the surface where the drug is gradually released without interference from gas bubbles. The in vitro drug release, buoyancy lag-time, detachment force and swelling index were evaluated. The in vitro drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied by gamma scintigraphy. The release of rosiglitazone maleate from the tablets followed the matrix first-order release model. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 h in the human stomach.

Mukesh C. Gohel et al., (2009), Developed venlafaxine hydrochloride-layered tablets for obtaining sustained drug release. The tablets containing venlafaxine hydrochloride 150 mg were prepared by wet granulation technique using xanthan gum in the middle layer and barrier layers. The granules and tablets were characterized. The in vitro drug dissolution study was conducted in distilled water. The tablets containing two lower strengths were also developed using the same percentage composition of the middle layer. Kinetics of drug release was studied. The optimized batches were tested for water uptake study. Radar diagrams are provided to compare the performance of formulated tablets with the reference products, Effexor XR capsules. The granules ready for compression exhibited good flow and compressibility when xanthan gum was used in the intragranular and extragranular fractions. Monolayer tablets failed to give the release pattern similar to that of the reference product. The drug release was best explained by Weibull model. A unified Weibull equation was evolved to express drug release from the formulated tablets. Lactose facilitated drug release from barrier layers. Substantial water uptake and gelling of xanthan gum appears to be responsible for sustained drug release. The present study underlines the importance of formulation factors in achieving same drug release pattern from threestrengths of venlafaxine hydrochloride tablets.

MA Naeem et al., (2010); Developed and characterized bilayer tablet formulations of tramadol HCl (TmH) and acetaminophen (AAP) microparticles by Coacervation via temperature change
was the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. The microparticles of the two drugs were prepared separately and then compressed into bilayer tablets. The physicochemical compatibility and stability of the tablets were determined by Fourier transform infrared spectroscopy (FTIR), x-ray diffractometry (XRD), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) while their mechanism and pattern of drug release were assessed by applying Higuchi, Zero order, First order and Korsmeyer-Peppas kinetic models. Bilayer tablets were subjected to accelerated stability studies for three months. FTIR, XRD, DSC and TGA data for the formulations indicate good compatibility and stability. Furthermore, accelerated stability studies confirmed the stability of the formulations. Controlled drug release from the microparticles and bilayer tablets was observed for 8 h and 12 h, respectively. The Higuchi model produced the best fit, with regard to release profile, for both drugs, with correlation coefficient (R2) of 0.966 and 0.960 for AAP and TmH, respectively. Microencapsulated TmH and AAP can be developed into suitable bilayer tablets that are stable and capable of releasing the drugs over 12 h.