2) LITERATURE REVIEW:

- **Shaikh et al. (2012)** reviewed different techniques for Bilayer tablet. Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines such as the Courtoy-R292F. Whenever high quality bi-layer tablets need to be produced at high speed, the use of an ‘air compensator’ in combination with displacement control appears to be the best solution.

- **Patel et al (2010)** studied challenges in the formulation of bilayered tablets. This article explains why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach in producing a quality bi-layer tablet under GMP-conditions. Especially when high production output is required.

- **Deshpande et al. (2011)** reviewed bilayer tablet technology as emerging trend. Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate (e.g. IR and ER) can be incorporated in a single unit. To develop a robust bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management.

- **Vaithiyalingam et al. (2010)** highlighted the material attributes, formulation design, process parameters that impact the performance and manufacturability of the multilayered tablets. (Vaithialingam et al., 2010)

- **Singh et al. (2007)** developed the bilayer tablet of propranolol hydrochloride by using superdisintegrant sodium starch glycollate for fast release and water insoluble polymer ethyl cellulose, eudragit RLPO and eudragit RSPO for sustained release.

- **Kaza and Nagaraju (2010)** developed the bilayer tablet of salbutamol and theophyline to enhance the patient compliance and prolong bronchodilation using HPMC K4M, HPMC K 100, which were found to be best in controlling the release. (Kaza and Nagaraju, 2010)
• **Surana et al. (2007)** developed the bilayer tablet of metoclopramide hydrochloride as IR layer using various disintegrants such as Ac disol, Explotab, Agar etc. and SR layer of Ibuprofen using HPMC K4M for the treatment of migraine.

• **Patel et al. (2007)** developed the mucoadhesive buccal devices of propranolol hydrochloride in the forms of bilayerd and multilayered tablets. The tablets were prepared by using Sodium carboxy methylcellulose and carbopol 1-934(CP) as bioadhesive polymer to impart mucoadhesion and ethyl cellulose to act as an impermeable backing layer. They formulated this formulation in order to avoid the first pass metabolism and to increase the bioavailability of (PRH) in bilayer form.

• **Hamaza et al. (2009)** designed directly compressed double layered tablets of lornoxicam, a highly potent NSAID with short half life that are characterized by initial burst drug release in the stomach and comply with the release requirement of SR product. The IR layer of lornoxicam contains hydroxy propyl-beta CD, which helps to enhance the dissolution and Xanthan gum was used in SR layer.

• **Maggi et al. (1999)** proposed the biphasic release system of slightly soluble drugs ketoprofen and praziquantel to enhance their dissolution rate by milling them with superdisintegrant. Bilayer tablet contain an immediate and sustained release layer. SR layer was prepared by using different concentrations of HPMC viz 10%, 16%, 22% with its different viscosity grades i.e. HPMC K4, K15, and K100M.

• **Khar et al. (2006)** developed the bilayer floating tablet 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 polymer s such as HPMC-K15, PVP -K30 and carbopol 934 alone or in combination with the drug.

• **Narendra et al. (2006)** developed an optimized gastric floating drug delivery system of metoprolol tartarate as model drug by using optimization technique. The bilayer tablet was prepared by using drug layered granules as an immediate dose. This was prepared by mixing metoprolol tartarate, starch, PVP, dicalcium phosphate using water as wetting agent. Sustained dose containing floating granulesw of MT were prepared by mixing the drug with excipients.
• **Wei et al. (2001)** developed a two layer floating tablet of gastric retention by using cisapride as model drug. Bilayer tablet was prepared by using granules containing 10% sodium bicarbonate, 50% starch 1500, 40% HPMC (K100M Cr) in 80% ethanol as wetting agent. Granules of cisapride were prepared by mixing the drug with excipients.

• **Ozdemir et al. (2000)** developed the bilayer tablet of furosemide, in which the first layer provided floating and contained the mixture of sodium bicarbonate and citric acid to form air bubbles and HPMC 4000 as a matrix material to retain the air bubbles. Second layer provided controlled release of active material and contained active material and HPMC 100 as hydrophilic matrix material.

• **Mandal et al. (2008)** formulated the tablet using HPMC as the matrix forming polymer and the tablets were evaluated by *in vitro* studies. Three different grades of HPMC (HPMC K4, K15, and K 100M) were used. All tablet formulations yielded quality matrix preparatons with satisfactory tableting propertis.

• **Rahman et al. (2012)** investigated Bi-layer tablets of tramadol hydrochloride by direct compression technique incorporating an immediate release layer and a sustained release layer. An immediate release layer was successfully designed to release the bolus dose instantaneously. Water soluble Xanthan gum, water insoluble Kollidon SR and Eudragit L 100 were used as carriers in the sustained release layer of the matrix tablet. Xanthan gum was found to be the most effective rate retarding agent compared to Kollidon SR and Eudragit L 100, when used at same ratio in the formulations.

• **Atram et al. (2009)** developed an optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate as a model drug candidate by optimization technique. A $3^2$ 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: $t_{50}$ (Y1), $Q_{12}$ (Y2) and $t_{50}$ (Y1), $Q_{12}$ (Y2), respectively.

• **Kumar et al. (2012)** investigated bilayer tablet containing Metoprolol succinate as sustained release and Ramipril as an immediate release layer. The sustained release part was formulated by using hydrophilic polymer HPMC K - 100 and HPMC K4M. As the polymer ratio increases the release rate of the drug decreases from the matrix tablet.
formulation is various physiological pH conditions. From this study it can concluded that Ramipril and Metoprolol can be formulated with Metoprolol as sustained release layer by using HPMC K-100.

- **Bagde et al. (2011)** made an attempt to reduce the frequency and units of dose administration, to prevent nocturnal heart attack and to improve the patient compliance by developing a Bilayer tablet having ER layer of Metoprolol succinate and IR layer of Ramipril. HPMC K100M and Sodium CMC were used for extended release of Metoprolol succinate. The Physically robust Bilayer tablets of Metoprolol succinate and Ramipril can be successfully formulated by using combination of polymers like HPMC K100M and Sodium CMC for metoprolol succinate ER layer.

- **Kannan et al. (2012)** designed and evaluated an oral bilayer tablet containing Metoprolol succinate as SR layer and hydrochlorothiazide as IR layer. Sustained layer were prepared by wet granulation method using different grades of HPMC (HPMCK4M and HPMC K100M) as hydrophilic polymers and IR layer prepared by direct compression. Combination of polymers namely HPMCK4M and HPMC K100M showed a controlled release of drug from sustained layer.

- **Brito Raj et al. (2011)** developed Bilayer tablet of Metformin hydrochloride (SR) with Metoprolol tartarate (IR) as a once daily formulation. The formulations of tablets (B1-B10) were prepared by using release retarding agents like HPMC K100, Eudragit S 100 for SR layer and super disintegrants like Crosspovidone, Sodium starch glycolate (SSG) for IR layer. All the formulations obey Zero order release kinetics and the mechanism of drug release was found to be nonfickian diffusion. Thus it may concluded that the once daily Bilayer tablet of Metoprolol Tartrate with sustained release.

- **Kumar et al. (2012)** developed bilayer tablets of Amlodipine besilate (IR) Metoprolol succinate (SR) for the management of hypertension. In the formulation of immediate release sodium starch glycolate were used as super disintegrant and was directly compressed. For sustained release portion HPMC polymers were used in granulation stage. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

- **Mujoriya et al. (2010)** developed and evaluated formulation of Metoprolol Succinate ER and Amlodipine Besilate using different polymer (HPMC, Methocel, Carbapol) with
different diluents (MCC, Cellulose Phosphate, Starch, Croscarmalose Sodium). The experimental work was divided into preformulation studies, formulation development, and evaluation. It can be concluded that a stable bilayer tablet of Metoprolol succinate ER and Amlodipine besilate can be prepared by using HPMC K 15 M and carbomer as a polymer.

- **Jayaprakash et al. (2011)** studied 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. Preformulation studies were performed prior to compression. It was found that the optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol succinate in 1, 4, 8, 20 hours respectively. However, Amlodipine besilate released 98.28% at the end of 30 minutes.

- **Rajendran et al. (2011)** carried out study to establish Bi-layer tablets containing Metformin HCl as sustained release and Pioglitazone HCl as immediate release layer. Sustained layer were prepared by wet granulation method using different viscosity grade of HPMC (HPMC K4M & HPMC K100M) as polymers and immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. The result showed that combinations of polymers namely HPMC K100M and HPMC K4M in sustained layer can control the release of drug. The formulations (P6M7) having immediate release layer produces immediate effect within 54 second followed by sustained release (97.35%) at 8 hrs and it comparable with innovator.

- **Wolfram et al. (2006)** studied problems associated with the preparation of a fixed dose combination drug comprising telmisartan and amlodipine, that can be best handled by means of a bilayer pharmaceutical tablet comprising a first layer of telmisartan, preferably in amorphous form, in a dissolving matrix, and a second layer of amlodipine in a disintegrating or erodible tablet matrix. The tablet according to the present invention provides a largely pH independent dissolution of the poorly water soluble telmisartan, thereby facilitating dissolution of the drug at a physiological pH level, and adequate stability and drug release of amlodipine. The tablet structure also overcomes the stability
problem caused by the incompatibility of amlodipine with basic constituents of the telmisartan formulation. (Pub No.: US 20060110450A1)

- **Patel et al. (2005)** The present invention provides a pharmaceutical composition in the form of a bilayer tablet comprising: 1. A first discrete portion which comprises a sympathomimetic drug, or a pharmaceutically acceptable salt thereof, and a first carrier base material which provides a sustained release of the sympathomimetic drug or pharmaceutically acceptable salt thereof, 2. A second discrete portion made with formulation B which comprises a piperidinoalkanol compound or a pharmaceutically acceptable salt thereof, and a second carrier base material which provides an immediate release of the piperidinoalkanol or the pharmaceutically acceptable salt thereof. The bilayer tablets exist lamination and have acceptable physical strength during the self life. (Pub No. US20050220877A1)

- **Friedl et al. (2005)** studied problems associated with the preparation of a fixed dose combination drug comprising telmisartan and amlodipine. In further aspect, the present investigation relates to an improvement in bilayer tableting technology and provides a method of producing a bilayer tablet comprising the steps of:
  
  **i) First layer composition:**
  a. preparing an aqueous solution comprising telmisartan, at least one basic agent and optionally, a Solublizer and/or a crystallization retarder,b. Spray-drying said aqueous solution to obtain a spray-dried granulate,c. Mixing said spray-dried granulate with a water-soluble diluent to obtain a premix,d. Mixing said premix with a lubricant to obtain a final blend for the first tablet layer,e. Optionally, adding other excipients and adjuvants in any of steps a. to d.
  
  **ii) Providing a second tablet layer composition by,**
  a. mixing and/or granulating a diuretic with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants,b. Admixing a lubricant to obtain a final blend for the second tablet layer,iii)Introducing the first or the second tablet layer composition in a tablet press,iv) Compressing said tablet layer composition to form a tablet layer,v) Introducing the other tablet layer composition into the tablet pre, and vi) Compressing both tablet layer composition to form a bilayer tablet. (Pub No. US 2005089575A1)
• **Abebe et al. (2012)** developed bilayer tablet comprising: 1) A metformin XR formulation or a reduced mass metformin XR formulation as the first layer, 2) and SGLT2 inhibitor formulation as the second layer, and 3) Optionally a film coating that covers both layers. The metformin XR layer (1000mg) comprises sodium carboxymethyl cellulose as binder and Hydroxypropyl methylcellulose 2208 is a preferred release modifier. The SGLT2 inhibitor layer comprises fillers: lactose anhydrous, microcrystalline cellulose 302, pregelatinized starch, and mannitol. A preferred disintegrant is crospovidone. Hydroxypropyl cellulose EXF is the preferred binder. *(Pub No. US20120282336A1)*

• **Guerrero et al. (2009)** solved need for a combination of simvastatin, lisinopril and folic acid in a single dosage form at optimal doses, by providing a bilayer tablet comprising the following two compartments:
  i) Comprising as an active ingredients a pharmaceutically acceptable simvastatin compound; and ii) Comprising as active ingredients a pharmaceutically acceptable lisinopril compound and pharmaceutically acceptable folic acid compound characterized by the fact that both compartments are isolated from one another. Simvastatin is highly sensitive to light and moisture. For this reason in the tablet of the present invention this compound is isolated in a different compartment to that occupied by lisinopril and folic acid. In a preferred aspect of the present invention, the tablet is obtained by direct compression. In a preferred aspect of the present invention, the tablet is obtained by wet granulation. *(Pub No.: US20090196922A1)*