A comprehensive literature search was carried out to capture information about dosage form, work done on similar type of systems, scientific journals, research papers, books; patent database was evaluated as enumerated below for drug of cardiovascular category such as Dipyridamole. Similarly a feasibility of this design would be investigated on another drug molecule from cardiovascular category such as carvedilol phosphate. This would help to create a platform drug delivery technology for drugs having pH dependant solubility.

From design perspective, the development of this concept involves as exemplified in introduction, a drug layering process using Wurster technology, followed by coating with modified release polymeric mixture coating to achieve the desired drug release, as the proposed concept defines control of release of acid from drug delivery system which is critical for in-situ solublization of active in the formulation.

Singh; et al. [2007] explained various modified release formulation drug delivery systems where solid formulations intended for targeted drug release into the lower gastrointestinal (GI) tract are beneficial for the localized treatment of several diseases and conditions, mainly inflammatory bowel diseases, irritable bowel syndrome and colon cancer. Also, because of their inherent potential to delay or avoid systemic drug absorption from the small intestine, colonic formulations can be utilized for chronotherapy of diseases which are affected by circadian biorhythms (e.g., asthma, hypertension and arthritis), and to achieve clinically relevant bioavailability of drugs that are poorly absorbed from the upper parts of the GI tract because of their polar nature and/or susceptibility to chemical and enzymatic degradation in the small intestine (e.g., proteins and peptides). The purpose of this review is to summarize the recent patent literature concerning various modified-release (MR) formulation technologies that are claimed to provide colonic delivery for a wide array of therapeutic molecules. These technologies either utilize a single or a combination of two or more physiological characteristics of the colon, which includes pH, micro flora (enterobacteria), transit time, and luminal pressure. Accordingly, these technologies may be grouped under four distinct classes: pH-controlled (or delayed-release) system, time-controlled (or time-dependent) system, microbially-controlled system, and pressure-controlled system. Among
these, formulations that release drugs in response to colonic pH, enterobacteria, or both are most common and promising.

H. Kranz, Brun & Wagner; et al. [2005] have studied a compound ZK 811 752, a potent candidate for the treatment of autoimmune diseases, demonstrated pH-dependent solubility. The resulting release from conventional mini matrix tablets decreased with increasing pH-values of the dissolution medium. The aim of this study was to overcome this problem and to achieve pH-independent drug release. Mini matrix tablets were prepared by direct compression of drug, matrix former (polyvinyl acetate/polyvinylpyrrolidone; Kollidon® SR) and excipients (lactose, calcium phosphate or maize starch). To solve the problem of pH-dependent solubility fumaric acid was added to the drug–polymer excipient system. The addition of fumaric acid was found to maintain low pH-values within the mini tablets during release of ZK 811 752 in phosphate buffer pH 6.8. Thus, micro environmental conditions for the dissolution of the weakly basic drug were kept constant and drug release was demonstrated to be pH-independent. Incorporation of water-soluble (lactose) or highly swellable (maize starch) excipients accelerated drug release in a more pronounced manner compared to the water-insoluble excipient calcium phosphate. Stability studies demonstrated no degradation of the drug substance and reproducible drug release patterns for mini matrix tablets stored at 25 °C/60% RH and 30 °C/70% RH for up to 6 months.

S Siepe, Lueckel, Kramer, Ries & Gurny; et al. [2006] have studied incorporation of weak acids as pH modifiers which enhances the release of weakly basic drugs in higher pH environments by reducing the micro environmental pH (pHM). The objectives of this study were: (a) to investigate the relationship between pHM, drug release, and pH modifier release and (b) to achieve simultaneous release of the drug and the pH modifier over the entire dissolution time (6 h, phosphate buffer, pH 6.8). Using Dipyridamole as a model drug, we investigated drug and acid release and determined the average pHM potentiometrically using tablet cryosections. The first approach was based on incorporating different concentrations of pH modifiers in conventional matrix tablets based on hydroxypropylmethylcellulose. Owing to its high acidic strength and low aqueous solubility, fumaric acid resulted in simultaneous release and maintained a constant acidic pHM. Secondly, press-coated matrix tablets, comprising an acidic reservoir, were found to be a valuable approach for retarding the diffusion of more water-soluble acids. Using the power law expression \( \frac{M_t}{M_\infty} = k t^n \) it became evident that the inclusion of acids increased drug release. Higher acid concentrations
tended to decrease \( n \) standing for the slope, whereas the release constant \( k \) increased. Furthermore, the medial check term parameters depended on the type of pH modifier used.

Siepmann, Lecomte, & Bodmeier; et al. [1999] have studied the effect of the composition of diffusion-controlled release devices (type and amount of plasticizer, type of polymer) on the drug diffusivity and the resulting release kinetics in a quantitative way. Diltiazem hydrochloride and theophylline were investigated in ethyl cellulose (EC) and Eudragit RS 100, plasticized with various amounts of acetyltributyl citrate (ATBC), acetyltriethyl citrate (ATEC), dibutyl phthalate (DBP), dibutyl sebacate (DBS), diethyl phthalate (DEP), and tributyl citrate (TBC). Thin drug-containing films (monolithic solutions) were used to determine the diffusion coefficients experimentally. The effect of the type and amount of plasticizer on the drug diffusivity was found to be significant, whereas the chain length of the polymer only played a minor role in the investigated systems. Interestingly, a quantitative relationship between the diffusion coefficient of the drug and the plasticizer level could be established. Based on these results, the release kinetics of diffusion-controlled drug delivery systems could be predicted. In this study, the release patterns from microparticles were calculated and the significant effect of the composition of the device on the resulting release rate was simulated. The latter could be effectively modified by varying the type and amount of plasticizer. Independent experiments verified the theoretical predictions. The practical benefit of the presented method is to calculate the required composition of diffusion-controlled drug delivery systems (monolithic solutions) to achieve desired release profiles.

Frenning, Tuno & Alderborn; et al. [2003] explained a mathematical model of drug release from coated pellets with a granular core. The model includes a dynamic description of all three main processes contributing to drug release from such a system, i.e. liquid inflow, drug dissolution, and liquid efflux caused by diffusion across the coating. The cumulative fraction of released drug has been shown to be determined by three rate constants, one for each process mentioned above, together with two dimensionless parameters. These parameters are related to the porosity of the pellet core and the solubility of the drug in the dissolution medium. The model has been validated by comparison with experimentally determined release profiles for pellets consisting of a granular core of microcrystalline cellulose containing dispersed salicylic acid, coated by a thin layer of ethyl cellulose.
A. Gursoy, D. Karakus, I. Okar; et al. [1999] have studied the preparation of Dipyridamole (DIP) alginate (alg) microspheres by different methods or the incorporation of tragacanth (trgh), pectin or Eudragit L-100 55 (Eud) in alginate microsphere formulations which did not provide a prolonged release of DIP at pH 1.2. Tabletted microsphere formulations containing alginate, tragacanth, pectin, sodium carboxymethyl cellulose (CMC), sodium starch glycolate (SSG), carrageenan (carrg) or Eud as diluents in different ratios, produced tablets with good physical properties which did prolong DIP release. The type, viscosity and the ratio of the diluent polymer, microsphere size and the compression pressure were found to be important factors to produce tablets with desired properties. No advantage of the tablets containing alg microspheres and granulated diluents was observed over the tablets containing powdered diluents.

P. Giunchedi, U. Conte; L. Maggi; A. La Manna; et al. [1992]; studied in their research article that after oral administration of basic drugs, the different pH values of the gastrointestinal tract can result in drastic changes in drug solubility, which can be very high at acidic pH values and dramatically low at neutral/basic pH, with consequent problems for the design of oral extended release formulations. In this paper, the preparation of an oral extended release formulation containing a basic drug is proposed, using Dipyridamole as model. Three-component modified release granules capable of moderating the drastic dissolution behaviour of Dipyridamole were prepared by loading a swellable polymer (cross-linked sodium carboxymethylcellulose) with both the drug and an enteric polymer (cellulose acetate phthalate or cellulose acetate trimellitate). In vitro dissolution tests of modified release granules in USP gastric fluid showed a modulation of the high dissolution rate of Dipyridamole at the acidic pH values, while in USP intestinal fluid a very marked improvement in drug dissolution was observed. Hydrophilic matrices containing the drug with the smoothed dissolution rate characteristics were prepared via mixing the granules with a gelling polymer (cellulose ether) and then tabletting the resulting mixture. In vitro release tests performed both at constant pH and with pH variation showed that the matrices are capable of providing extended drug release in both acidic and neutral/basic media.

Naonori Kohri & others; et al. [1992] studied that the solubility of Dipyridamole at pH 2.5 was about 6000-fold greater than that at pH 7.0. A commercial powder of Dipyridamole showed pH-dependent dissolution. Two kinds of sustained-release granules of Dipyridamole were prepared. The release rate of pH-dependent sustained-release granules was controlled by ethyl cellulose (EC) and decreased with increasing medium pH. The release rate of pH-
independent sustained-release granules was regulated by carboxymethylethylcellulose (CMEC), hydroxypropyl methylcellulose (TC-5) and Eudragit RS100, and was not influenced by varying pH of the medium.

Ulrich Heigoldt and other; et al. [2010] have studied in vitro dissolution testing during early development of modified release (MR) formulations to provide predictive estimates of drug release in respect to in vivo performance of a drug product. However, there are enormous challenges in MR drug development to establish proper dissolution conditions for a predictive test. To overcome limitations of dissolution testing at constant pH, a modified USP apparatus 2 was developed, combining biphasic dissolution with a pH-gradient in the aqueous dissolution medium. Quasi sink conditions in the aqueous phase were introduced by the removal of dissolved active via distribution to an organic phase. Results from in vitro drug-release studies and in vivo absorption studies of four MR formulations made by different technologies comprising the pH-dependent poorly soluble drugs, Dipyridamole and the investigational drug BIMT 17, indicated that dissolution testing using the biphasic approach enabled an improved forecast of the in vivo behaviour and bioavailability of modified release formulations compared to conventional dissolution testing at pH 1, pH 5.5, or pH 6.8.

D. Beten, Amighi & Moes; et al. [1995] studied controlled-release drug-polymer co evaporates on an industrial scale, omitting the recovery problems and the milling and sieving processes encountered when co evaporates are prepared by the conventional solvent-evaporation technique using Dipyridamole as a model drug.

Siepe, Lueckel, Kramer, Ries & Gurny; et al. [2008] studied tailor-made, pH-controlled matrix minitablets based on different HPMC types were developed comprising the weakly basic drug Dipyridamole. The incorporation of pH modifiers, i.e., fumaric and succinic acid, enhanced the drug release at pH 6.8. Assessing the drug release, acid release, and the micro environmental pH ($pH_M$) provided detailed understanding of pH-controlled mini-matrices. The extent and duration of $pH_M$ alteration was more pronounced in presence of fumaric acid. Minitablets based on the fast dissolving Methocel K100LV ($\leq 100$ cps) showed simultaneous release rates of Dipyridamole and fumaric acid with a constant low average $pH_M$.

A comprehensive patent search was carried out on the selected drug molecule to understand patent limitations and develop an out of scope formulation strategy following list enumerates
critical active and inactive patents on the selected molecule, this is being used as a reference to initiate development in this direction.

Yang Wang Huailin Liu; et al. [2010]; CN102210693 studied method for preparing aspirin and Dipyridamole multilayer tablets. The invention provides a method for preparing aspirin and Dipyridamole multilayer tablets, which is characterized by comprising: preparing Dipyridamole sustained-release tablet cores by tabletting; and coating a stomach soluble insulation layer, an aspirin quick-release layer and a stomach soluble protective layer in turn. The method has the advantage that aspirin common release and Dipyridamole sustained-release compound preparations are prepared by using conventional pharmaceutical equipment.

Pasahn Manohar; et al. [2010]; EP2361615 (A1) discussed and proposed Dipyridamole prolonged-release tablet which essentially claims Intra gastric floating tablet, comprising a) in the Intragranular phase: a pharmaceutically active ingredient and a water-swellable polymer, and b) in the extra granular phase: hydroxypropyl methyl cellulose (HPMC), wherein the tablet contains a gas generating agent.

Zhang Jun; et al. [2011]; CN102178671 (A) discussed and proposed in his patent Aspirin and Dipyridamole gastric floating tablets and preparation method thereof

Ben-menachem avshalom; et al. [2010] WO2010036975 (A2) & US 2010/0080846 A1 have developed and discussed - Dipyridamole and acetyl salicylic acid formulations and process for preparing the same & broadly claims a pharmaceutical formulation comprising: (i) pellets comprising Dipyridamole, and (ii) pellets comprising acetylsalicylic acid, wherein components (i) and (ii) are physically separated.

Ahmed Salah U; et al. [2009] WO2009097156 (A1) & US2009196935 (A1) have exemplified & enumerated pharmaceutical capsules comprising extended release Dipyridamole pellets and broadly claims A pharmaceutical capsule comprising: a Dipyridamole extended release pellet comprising: (i) a core comprising a first organic acid, wherein the core has an aspect ratio of 1.2 or greater; (ii) a first coating layer comprising a second organic acid and a binder, wherein the first coating layer encompasses the core; (iii) a second coating layer comprising a binder, wherein the second coating layer encompasses the first coating layer, and wherein the second coating layer is substantially free of an organic acid; (iv) a drug layer comprising Dipyridamole and a binder, wherein the drug layer
encompasses the second coating layer; and (v) an extended release layer comprising an enteric polymer, wherein the extended release layer encompasses the drug layer; wherein the Dipyridamole is not in contact with the first organic acid and the second organic acid.

Guangyan Wu; et al. [2008] CN201299813 (Y) - have exemplified tablet capsule containing aspirin tablet and Dipyridamole tablet, he also discusses various methods for making tablet formulation of Dipyridamole and aspirin

Rongsheng Ma; et al. [2008] CN101259132 (A) have discussed aspirin Dipyridamole sustained-release capsules and production method, The invention discloses Aspirin-Dipyridamole Sustained-Release Capsules and a production method thereof, the capsule contains an Aspirin film coated tablet and Dipyridamole Sustained-Release pellets, with each Aspirin film coated tablet contains 12.5mg of Aspirin, and the content of Dipyridamole Sustained-Release pellets in each capsule reach 0.1g. The production method comprises the preparing of Aspirin film coated tablet and Dipyridamole Sustained-Release pellets and encapsulation; the production method of the invention is rational, Aspirin is preformed directly from powder, thus controlling salicylic acid in a comparatively low level, which is harmful to human body, and improving the stability of the medicine.; The product of the invention is a medicine used for anti-platelet aggregation and anti-coronary artery dilatation, which is applicable to the sufferers of ischemic stroke that has an attack of transient cerebral ischemia or is caused by thrombus, and can reduce the danger of stroke or recurrence of stroke

Gilbert James C; et al. [2008] US2008188497 (A1) studied combination of - Dipyridamole, Acetylsalicylic Acid, and Angiotensin II Antagonist Pharmaceutical Compositions and broadly it claims A pharmaceutical composition comprising a therapeutically effective amount of: (a) Dipyridamole or a pharmaceutically acceptable salt thereof, (b) acetylsalicylic acid; and (c) an Angiotensin II antagonist, kits containing these three compounds, and methods for preventing stroke or reducing the risk of stroke or secondary stroke in a patient in need thereof by administering an effective amount of these compounds to the patient

Ming Zhang; et al. [2008] CN201157559 (Y) have studied & enumerated - Aspirin Dipyridamole dual-release capsule fine tablet & The utility model relates to an aspirin Dipyridamole two-release capsules slow-release micro tablet, which comprises a capsule body 1, an aspirin immediate-release micro tablet 2 filled in the intra-cavity of the capsule
body 1 and a Dipyridamole slow-release micro tablet 3. The micro tablet has simple preparation technology and does not need to be compressed for several times.

**Minutza Leibovici; et al. [2008] HK1104791 (A1) & US20070184110A1** have studied and exemplified Dipyridamole extended-release formulations and process for preparing same the invention is directed to a Dipyridamole formulation comprising an extended release formulation of Dipyridamole and a pharmaceutically acceptable carboxylic acid, wherein the formulation is in a tablet solid form having a diameter of about 1.5 mm to about 3 mm. Optionally, the formulation may further comprise an immediate release acetylsalicylic acid formulation.

**BAIZHONG XUE; et al. [2009] CN101428030 (A)** - have studied and claimed Compound Dipyridamole/acetophen sustained-release capsule and preparation thereof & the invention relates to compound Dipyridamole/aspirin sustained-release capsules and a preparation technique thereof. The invention is characterized in that sustained-release micropill technique is applied to prepare two components: sustained-release Dipyridamole and quick acting aspirin into compound preparation which is used for treating cardiovascular and cerebrovascular diseases. Different dosage at different times and multiple taking of the two medicines are changed into twice a day, thereby being convenient for the patient to take. Aspirin can reduce the dosage of Dipyridamole and reduce the side effect thereof of blood pressure decrease; Dipyridamole can improve the bioavailability of aspirin, and increase the efficacy on preventing and treating cardiovascular and cerebrovascular diseases. By combining Dipyridamole and aspirin, the effects of the two medicines on inhibition of platelet aggregation and thrombosis in different links can be completely exerted. The efficacy of the compound preparation is obviously superior to that of single prescription preparation.

**Patil Atul et al [2008] EP1894561 (A1)** - have studied on Dipyridamole pharmaceutical compositions Pharmaceutical compositions which comprise a pharmaceutically inert core coated with an intermediate coating, a coating thereon comprising Dipyridamole, and a further coating comprising a drug release modifier.

**Leibovici; Minutza; et al. [2007]; US 2007/0184110 A1** have incorporated in its patent application a Dipyridamole formulation comprising: an extended release formulation of Dipyridamole and a pharmaceutically acceptable carboxylic acid, wherein the formulation is in a mini-tablet solid form having a diameter of about 1.5 mm to about 3 mm.
Eisert, et al. [1995]; US6015577 claims a pharmaceutical composition for oral administration comprising: a) Dipyridamole pellets, each such pellet having a core consisting of a pharmaceutically acceptable acid excipient, a first coating surrounding the core comprising Dipyridamole and polyvinylpyrrolidone, and a lacquer coating, on top of the first coating, comprising methacrylic acid/methylmethacrylate copolymer and hydroxypropylmethylcellulose phthalate; b) an acetylsalicylic acid tablet, comprising an acetylsalicylic acid core and a coating comprising sucrose; and, c) a capsule, for containing the Dipyridamole pellets and the acetylsalicylic acid tablet; the quantities of the various components being adjusted so that the final dosage form comprises about 25 mg of acetylsalicylic acid and about 200 mg of Dipyridamole.

Gruber; et al. [1980]; US 4,367,217 disclosed a composition where Dipyridamole and carboxylic acid are combined together into spheroid particles which are surrounded with a dialysis membrane consisting essentially of acid-insoluble lacquers soluble in intestinal juices. The '217 patent teaches that "if the total dose is divided into hundreds of independent, small, sustained release forms, then a statistically uniform, largely consistent passage of this sustained release form through the gastro-intestinal tract is provided." The '217 patent goes on to explain that "the effects of the differences in the pH gradient and the gastro-intestinal motility of individual patients on the Dipyridamole blood level behavior are thereby largely compensated for" and that "realization of the principle of a certain pH-dependent control of release therefore necessitates in the case of Dipyridamole the use of spheroid particles such as rounded granulates or pellets."

Weithmann, et al. [1985] US4,694,024 disclosed that "surprisingly" it was found that administration, successively with a time interval, of Dipyridamole and O-acetylsalicylic acid in a particular sequence with a time interval made "an extremely great improvement in the therapy of diseases which are caused or characterized by impaired blood functions or impaired constituents of blood." The '024 patent states that "[t]he combination [of] products according to the invention make it possible for the pyrimido-pyrimidine component [Dipyridamole] to be released (be bioavailable) first, i.e. before the acetylsalicylic acid." This was based upon the observation that "the simultaneous administration of pyrimido-pyrimidine, such as Dipyridamole, and acetylsalicylic acid leads only to an insignificantly more potent action than is obtained on administration of acetylsalicylic acid alone." Furthermore, the '024 patent states that "the therapeutic effect cannot be increased further by
increasing the relative acetylsalicylic acid weight content in the combination according to the invention to values above 2," e.g., Dipyridamole to aspirin ratio of 1:2.

Ens, et al. [2005] US 6967083 disclosed a method for determining a minimum optimum aspirin dose for inhibiting platelet activation in a patient, said method comprising: a) administering to a patient a known dose of aspirin; b) collecting a urine sample from the patient; c) determining an amount of a thromboxane B.sub.2 metabolite in the urine sample; d) determining an amount of creatinine in the urine sample; e) normalizing the amount of thromboxane B.sub.2 metabolite to the amount of creatinine to create a thromboxane B.sub.2 metabolite/creatinine ratio; f) optionally repeating steps a) through e) with different known doses of aspirin to determine the optimum dose of aspirin which is the dose that provides less than about 1000 pg thromboxane B.sub.2 metabolite/mg creatinine.

Gilbert; James C.; et al. [2008] US 2008/0188497 disclosed a pharmaceutical composition comprising a therapeutically effective amount of: (a) Dipyridamole or a pharmaceutically acceptable salt thereof, (b) acetylsalicylic acid; and (c) an Angiotensin II antagonist, kits containing these three compounds, and methods for preventing stroke or reducing the risk of stroke or secondary stroke in a patient in need thereof by administering an effective amount of these compounds to the patient.

Soula; Gerard; et al. [2010] US 2010/0009005 A1 disclosed The invention relates to pharmaceutical compositions of acetylsalicylic acid-based microcapsules to selectively inhibit the COX in the portal vein and/or in the liver to reduce the production of thromboxane. Further, the pharmaceutical composition minimizes COX inhibition in the systemic circulation to optimize the inhibition of platelet aggregation. Certain embodiments also address methods of prevention and/or treatment of these diseases, using these oral compositions such as enhancing the safety of antithrombotic treatments. Other embodiments contemplate oral pharmaceutical compositions that combine acetylsalicylic acid with anti-platelet aggregation drugs, without inducing gastric side effects.