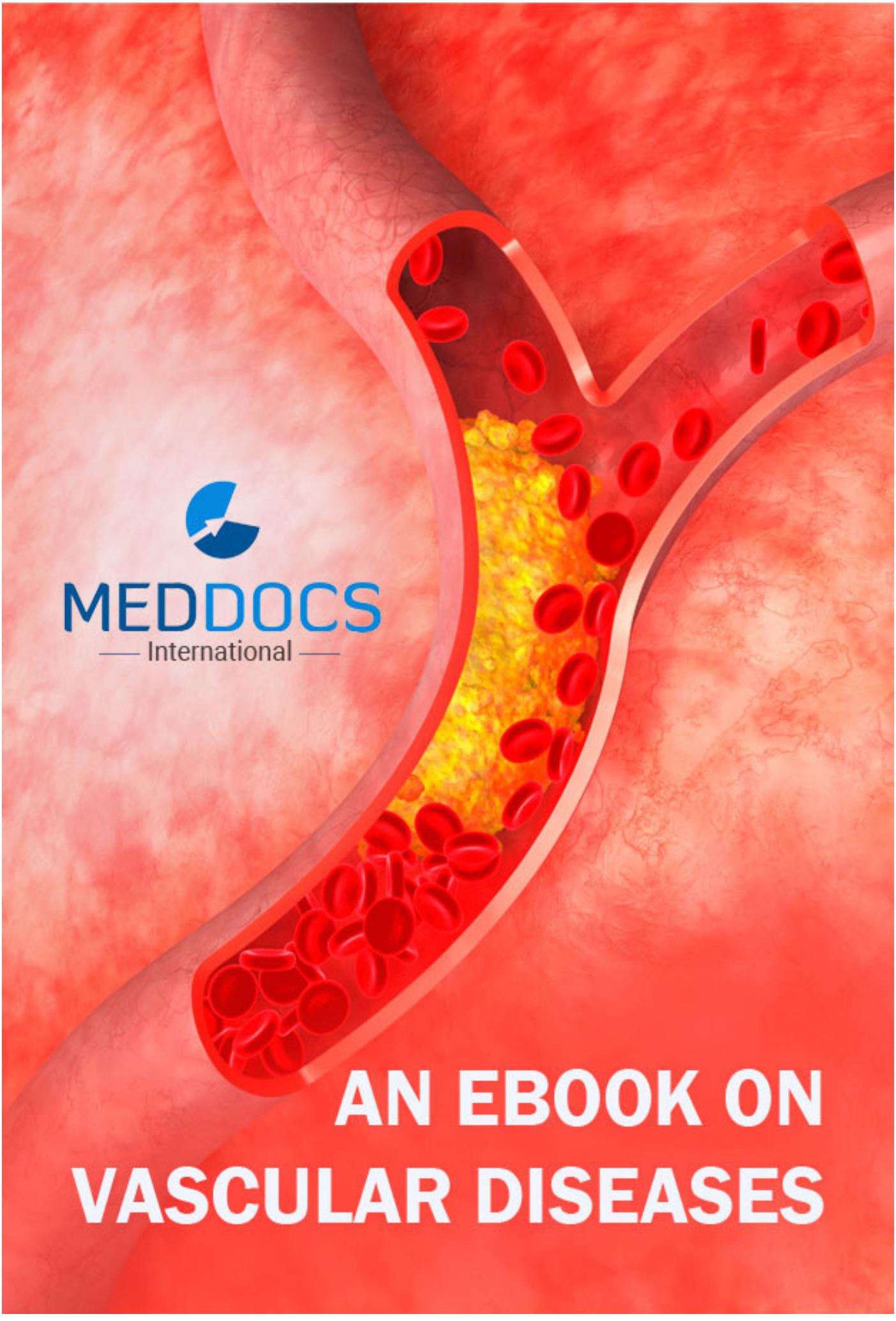

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Combined Amlodipine Besylate-Simvastatin Matrix Tablet Formulation for Co-Occurring Hypertension and Dyslipidemia

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Abstract

Hypertension and atherosclerosis, due to dyslipidemia are the major risk factors of Cardiovascular Diseases (CVDs) and are among the leading causes of death world over. The co-occurrence of hypertension and dyslipidemia requires rigorous management using multiple therapy, a reason for low patient compliance. Attempts have been made to combine amlodipine besylate (antihypertensive) and simvastatin (lipid-lowering drug) in a fixed-dose matrix tablet for their differential release, i.e., amlodipine immediately and simvastatin after 8 h. Differential release for both drugs has been achieved by using selective polymers for each drug. In a sequential study, the release controlling parameters have been identified using risk assessment approach followed by optimized through the design of experiment for accomplishing optimal prolonged release. Eudragit® RSPO modulates amlodipine besylate release, though a first order diffusion-controlled release instead of the desired zero order. A pH sensitive polymer, Eudragit® RS 100 retards the simvastatin release. Among the above the optimized formulations of amlodipine and simvastatin, with the targeted release has been formulated in a fixed-dose combination. The fix dose combination of amlodipine and simvastatin shows the desired dosage form characteristics. The same formulation in a pharmacokinetic evaluation revealed a speedy amlodipine besylate absorption while a delayed absorption of simvastatin for 6 h, close to targeted interval of 8 h.

Hypertension, dyslipidemia and cardiovascular diseases

Hypertension, one among the major risk factors for Cardiovascular Diseases (CVDs) is a leading cause of death globally. CVDs represent the collective disorders which involve the heart and vessels. Hypertension brings alteration in arteries structure and also a cause of elevated risks for the other associated diseases. It accounts for 51% and 45%, deaths in the world, respectively of stroke and ischemic heart disease. Hypertension is a major cause of death in the middle income European countries (54%) and the southeast Asia (37%) [1]. The risk factors for the heart diseases and stroke include the behavioral factors, such as the unhealthy diet, physical inactivity and tobacco use. The above behavioral factors may cause hypertension, rise blood lipids, and blood glucose, also known as the intermediate risk factors [2].

Dyslipidemia increases the risk for vascular diseases and is the leading cause of atherosclerosis. CVDs may also involve atherosclerosis. The one third of ischemic heart disease world over is due to elevated low density lipoprotein, cholesterol levels [1]. The chance for the co-occurrence of hypertension and dyslipidemia is high. According to National Cholesterol Education Program guidelines, an aggressive management of both hypertension and dyslipidemia is required when the both of above co-occur or in the presence of diabetes [3].

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Management of hypertension and dyslipidemia

Thiazide diuretics are extremely useful in lowering of CVD events secondary to reduction of blood pressure. The clinical data support that Angiotensin Converting Enzyme inhibitors (ACE), angiotensin receptor blockers, and beta blockers help reducing complications of hypertension [4]. The calcium channel blockers, initially approved for the therapy of angina pectoris, are useful in treating pulmonary and systemic hypertension and other conditions. The calcium channel blockers selectively block the calcium channels and thereby, inhibits the entry of calcium into the variety of cells. These also hamper the calcium dependent excitatory processes by impeding the depolarizing current. Furthermore, calcium channel blockers induce vasodilation, a basis for their use to manage hypertension [5]. Amlodipine besylate (Figure 1), a dihydropyridine compound, is a significant member of this class.

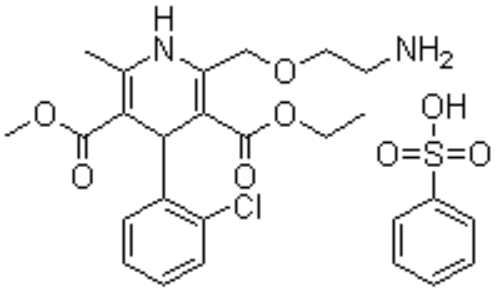

Figure 1: Chemical structure of amlodipine besylate (Taken from Chemblink.com).

Amlodipine besylate monotherapy in twice daily dosing is effective, safe and without significant adverse effects [6]. Due to high co-existence of hypertension and dyslipidemia together [7], anti-hypertensives and lipid lowering agent are commonly prescribed together as free combination. There are several cholesterol lowering classes including HMG CoA reductase inhibitors (Statins), bile acid sequestrants, nicotinic acid and fibric acid derivatives. Statins reduce stroke and other cardiac events by reducing Low Density Lipoprotein Cholesterol (LDL-C) [8].

A report states that the cholesterol (free and esterified) is synthesized the most when the dietary intake is least, i.e., during night. The above report raised a question for the dosing time of statin – that is whether the administration of statins are beneficial in the morning or evening [9]. Somewhat a greater LDL-C reduction occurs on administration of statins at night comparative to their intake in the morning, may be ascribed to a high first pass effect and a short half-life of the statins [10]. The dose-time dependent pharmacodynamics is reported for the lovastatin, fluvastatin, simvastatin and pravastatin [11]. The lowering of serum concentration of LDL-C by atorvastatin and rosuvastatin is not affected with the dosing time, primarily owing to a longer half-life and their metabolites [12].

Statins are the drugs of choice for the primary and secondary cardiovascular events in type-2 diabetes mellitus, though without clear demarkation of superiority one over the others among atorvastatin, lovastatin, fluvastatin, simvastatin and pravastatin [13]. Nevertheless, therapeutic equivalence meta-analysis exhibited minor clinical differences in between several statins for lowering LDL-C [14]. Rosuvastatin has been found to reduce LDL-C levels < 100mg/dl in 53-80% patients as compared to 18-70% by atorvastatin, 8-53% by simvastatin and 1-8% patients with pravastatin [15]. Simvastatin, in another study is reported to be less effective than atorvastatin in lowering total cholesterol, LDL and triglycerides, however is safer compared to atorvastatin by decreasing fibrinogen and increasing High Density Lipoprotein (HDL) [16]. Thus, simvastatin is a component of the heart health program and used primarily as prophylactic drug in moderate coronary artery disease. Simvastatin (10mg) has been a pharmacy-only over-the-counter medicine in the United Kingdom, since 2004. At 10 mg dose, simvastatin approximately reduces 30% of LDL cholesterol levels which reduces 33% risk of the major Coronary Artery Disease event after three years [17]. Simvastatin is an inactive lactone (Figure 2), which is hydrolyzed in the body to β-hydroxy acid, which is an inhibitor of HMG CoA reductase.

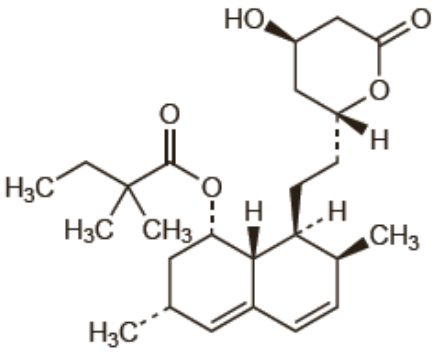

Figure 2: Structure of Simvastatin (Taken from Martindale edition 36).

Compliance issue with antihypertensive and lipid lowering monotherapy

The prescription of numerous free drug combinations is a cause of non-compliance in patients, along with some other causes [18]. Similarly, since the hypertension and dyslipidemia co-occur, treatment of the both conditions require the prescription of free drug combination which causes a low patient compliance. Drug compliance can be enhanced by adopting a multifaceted approach of patient counselling regarding awareness about the benefits of achieving target LDL levels and others factors [19] and presenting two or more drugs as Fixed Dose Combination (FDCs) in a single dosage form [20].

The detail is given in proceeding section. The FDCs must meet the following criteria; (A) it must target multiple co-existing conditions, (B) each component in FDC should contribute to the desired effects, (C) the dose of each component should effective and safe and (D) FDC should be developed for the diseases requiring concurrent therapy with clear benefits [21].

FDC for chronic ailments such as hypertension are of significant importance as they improve compliance by reducing the pill burden. FDCs has been reported to reduce risk of medication non-compliance 24% as compared to the free drug combination regimen [22]. The FDCs of antihypertensive amlodipine besylate and antilipidemic atorvastatin is currently marketed by Pfizer under the brand name Caduet®. It has been reported that polypill having antihypertensive, antilipidemic agent along with aspirin and folic acid have potential to reduce 80% of CVD risk and can be taken by all patients above aged 55 suffering from cardiovascular disease [23].

In current practice, amlodipine besylate and simvastatin are oftenly prescribed concomitantly to overcome CVD risk by re-

ducing blood pressure and LDL-C. Thus, amlodipine besylate and simvastatin fixed dose combination is logical and meets the criteria for FDCs. Hence, herein a fixed dose matrix tablet formulation of above drugs is reported. The simultaneous administration of both drugs is forbidden according to earlier reports [24]. The desirability is to achieve differential release of drugs; amlodipine besylate zero order release and to hold release of simvastatin for 8 h by employing different polymers. The developed fixed dose formulation is expected to achieve enhanced patient compliance.

Fixed dose formulations for hypertension

Multifaceted regimens for treatment and polypharmacy are among the major risk factors in identification for noncompliance in treatment. Patient compliance, as indicated earlier can be increased by using FDCs which are preferable to reduce the pill burden (polypharmacy). In treatment of hypertension, range of noncompliance has been reduced 24% in FDC when it is compared to the free drug combination treatment. The plasma concentration of simvastatin has been reported to be raised when given with verapamil and diltiazem, a calcium channel blocker as free drug combination regimen [25].

Similar results were observed in case of lovastatin with diltiazem [26]. Thus, with a favorable clinically relevant drug-drug interaction between the FDC components could be side benefit for FDC for dose reduction of at least one of the components [27]. For instance, in free drug combination, a study has revealed increase in peak plasma concentration (C_{max}) and area under curve (AUC) of simvastatin on concurrent administration with amlodipine besylate without decreasing the level of cholesterol [28]. Cytochrome P450 CYP3A4 enzymes metabolize simvastatin and amlodipine besylate. The strong CYP3A4 inhibitors, i.e., cyclosporine increases the risk of myopathy when it is given with simvastatin, while no such kinds of effects have been shown when weaker CYP3A4 inhibitors such as calcium channel blockers are administered with simvastatin. Non-concurrent dosing should be preferred, if patient requiring both amlodipine and simvastatin [24].

Nevertheless, the above issue could be circumvented in a FDC which furnishes a differential release profiles amlodipine and simvastatin with an appropriate gap. Continuous amlodipine besylate release in plasma with zero order minimizes the potential peak through functioning in plasma. While to get advantage of effective reduction of cholesterol at night, a delayed releasing simvastatin (colon segment as shown in Figure 5), as a simple matrix tablet formulation combining with amlodipine using blend of pH dependent and independent polymers. Delayed release of simvastatin at pH 7 is expected to reduced its side effects. Furthermore, to treat local disorder such as colon drug delivery provides less aggressive environment to a drug the least enzymatic activity. Time for drug absorption was increased due to increased transit time of the colon (approx. 78 h). Several methods and routs are used for site specific drug delivery systems, i.e., control release drug delivery, time dependent formulations, but the pH dependent polymer approach is more preferred [29].

Controlling drug release through polymers

Polymers have large molecular weights due to repeating units in their chain. A wide variety of different polymers are used in pharmaceutical industries such as natural polymers (chiston, xanthan gum, starch), semisynthetic (hydroxyl propyl methyl cellulose, hydroxyl ethyl cellulose, methylcellulose etc.) and synthetic (polymethacrylates, polyacrylic, polyglycolic, etc.). These polymers are used to impart different properties such as use as binder, enteric coatings, site specific drug delivery, matrix formers for control release delivery and as bioadhesive materials [30]. Modifying or controlling drug release provides various advantages including increased effectiveness through site specific drug delivery, reduced frequency of dosing, and reduced dose or uniform drug delivery. Dissolution or diffusion controlled drug release system are more widely and commonly used for controlling the drug release [31].

Both pH dependent and independent polymers are effectively used to control drug release in tablet dosage forms. Polymers may be (polyvinyl chloride, polyvinyl acetate, polyvinyl pyrrolidone) or copolymers (ion exchange resins, Carbopol, polyethylene-co-vinyl acetate, Eudragit® and Kollicoat® series). Eudragit® are available in powder, pellets, organic or aqueous dispersion, used as a copolymers having methyl methacrylate backbone. Eudragit E, L and S have pH specific solubility while Eudragit RL and RS are not soluble at any specific pH due to very small quaternary amine fraction as compared to that of methyl methacrylate. Due to hydrophilic nature of quaternary ammonium groups, it controls the water uptake, swelling index and permeability of this polymer. Eudragit RL is more soluble than Eudragit RS due to presence of quaternary ammonium group. Both of these polymers can be blended to achieve the required release profiles [32]. Dissolution media of these polymers help them in movement of drug in and out of swollen matrix. Presence of quaternary amine in these polymers helpes to control the permeability through the matrix [30]. He structure of Eudragit® RL, RS, L and S is given below in Figure 3.

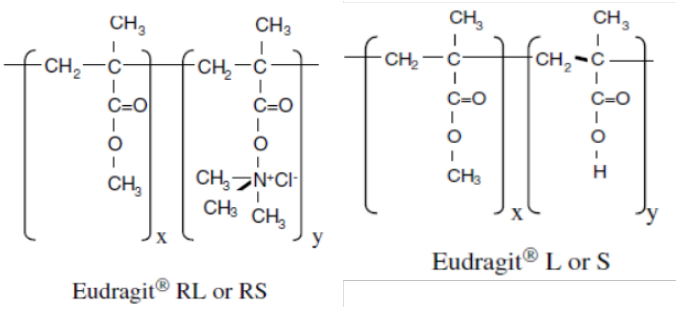

Figure 3: Chemical Structure of Eudragit RL, RS and S (Taken from [29]).

The Eudragit polymers are dissolved in organic solvent to maintain their pH as they are used for target released preparation, in which pH sensitivity is important parameter when used as a binder solution and as a dry form to achieve its sustained release effect [33]. This binding capacity of Eudragit may be obtained by mixing it in dry form and granulating with organic solvent, which enhances its solubility as well. Localized coating on granules of polymer surface may also have effect on the solubility in addition to binding [34]. Sustained released matrix tablets of Eudragit polymers have already been formulated. Eudragit® RLPO and RSPO are directly compressible forms of Eudragit® polymer, have been used to develop sustained release formulation by direct compression [35] or in combination with other hydrophilic polymers [29].

Matrix tablet formulations

The multiparticulate [36] or matrix tablet approach is in use for preparation of controlled release tablet formulations. Polymer matrix embedded drug is one of least complex approach

for controlled drug delivery system [37]. The Eudragit® matrix structures polymers are inert and exhibit pore diffusion drug release. The direct compression and granulation methods are employed for formation of matrix structures. The major types of matrix systems are plastic, hydrophobic and hydrophilic matrices. The plastic matrix system being inert and exhibiting enhanced drug embedding capability is used extensively. The potentially erodible hydrophobic systems control drug release by erosion and pore diffusion [38]. On hydration hydrophilic matrix systems on surface develop the gelatinous barrier which control the penetration of liquid into matrix and facilitate the release of drug from matrix [39]. Eudragit® polymer can be used for various parts of the gut according to required pH Figure 4.

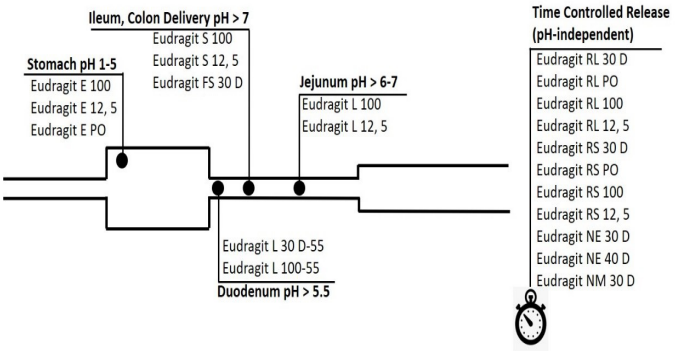

Figure 4: Eudragits for different pH of gut segments gut and time controlled release (adopted from Evonik Industries).

Formulation design

Pharmaceutical formulation is integrated system of various inputs (factors) and outputs parameters (properties). The properties of a dosage form depends upon various factors. During dosage form development at a time one variable (factor) is changed (OFAT) and its impact on dosage form properties is evaluated by keeping constant other factors using number of experiments [40]. The conventional OFAT strategy have many flaws including factor interactions ignorance and evaluates only small number of the total feasible factor space [41]. In addition, huge experimentation includes substantial cost and time. and, The process development and optimization should be achieved with lesser experiments [42]. For instance, the suitable drug to polymer ratio to obtain the required release profile can be adjusted by Design of Experiment (DOE) approach.

Design of experiment (DOE) for formulation design

Statistical techniques have now been increasingly employed to improve formulation design [43]. DOE is one of the above approaches and has worked to optimize the sustained release formulations. All types of DOE are now being used for development of pharmaceutical products and optimization of processes. To develop the validated predictive model suitable experimental design selection and statistical approach is required [44]. DOE flow diagram in general is presented in Figure 5. The pilot study can be achieved by conventional screening design, while DOE produce breakthrough designs for predictive modeling [45].

In the optimization phase, experiments on the predicted levels is designed by optimum factors' levels using Response Surface Methods (RSM) Figure 6. DOE is based on multiple approaches including RSM, regression and ANOVA [46]. DOE approach utilization is not only limited to process and formulation and optimization of variety of drug delivery systems [47], but it can also illustrate matrices swelling and erosion behaviors i-e HPMC [48] and to evaluate the polymer source variation impact [49]. DOE has employed for optimizing and assessing variety of quality attributes factors affecting dosage form [50].

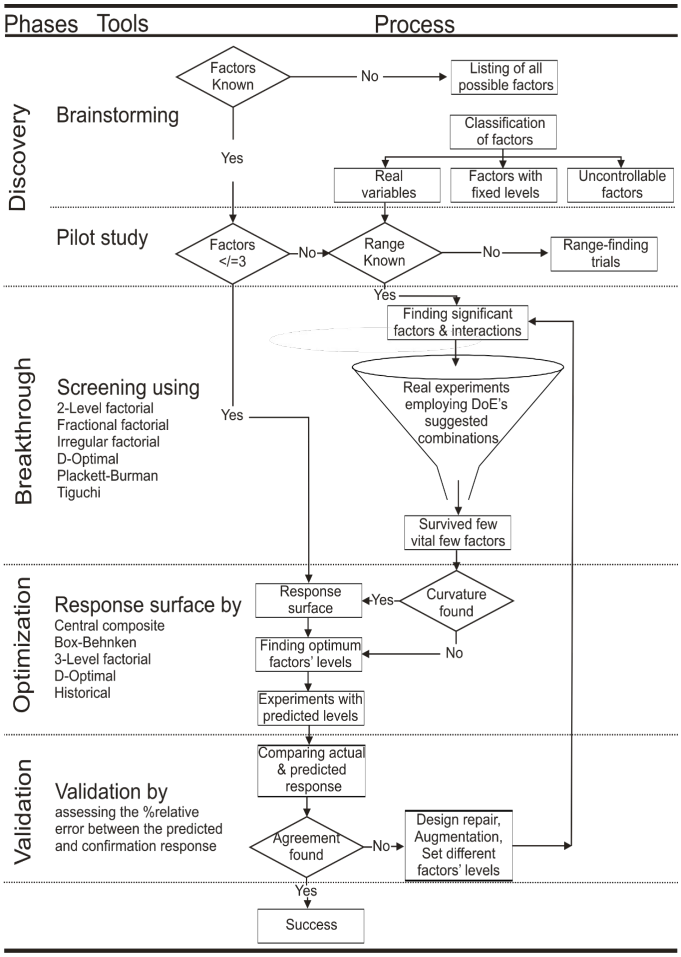

Figure 5: Strategy of experimentation.

Pharmacokinetic assessment

Pharmacokinetic describes the fate of a drug in biological fluids followed by its administration [51]. It involves compartmental approach in which body is considered as one-compartment model and two-compartment model [51]. The non-compartmental method does not consider the body as a compartment. The pharmacokinetic parameters required to study characteristics of a dosage form include the maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), total exposure ($AUC_{0-\infty}$), area under the first moment of plasma level time curve ($AUMC_{0-\infty}$), mean residence time (MRT), absorption rate constant (K_{abs}), elimination rate constant (K_{elim}), elimination half-life ($t_{1/2}$), the volume of distribution (Vd), volume of distribution at the steady state level (V_{ss}) and total clearance (Cl_T). It has been reported QbD-based optimized formulation in which Eudragit® RSPO-dicalcium phosphate (DCP) blend was used to control the release of AML-B for 8 h and DCP and Eudragit® RS 100 withheld release of SIM release for 8 h after release of AML-B from optimized FDC tablet formulation Figure 6 [52].

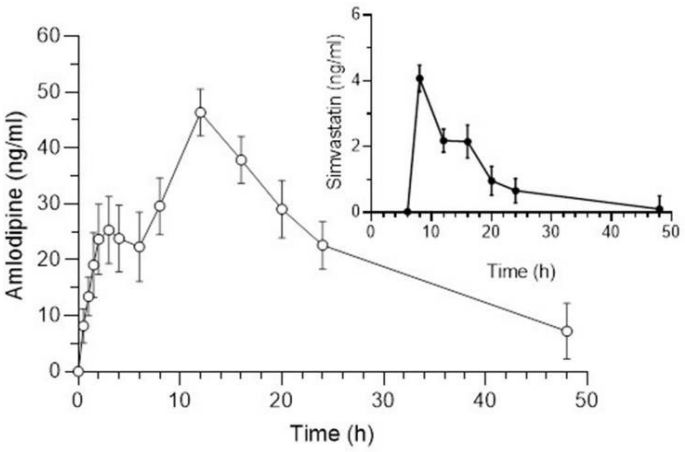

Figure 6: Mean plasma concentration vs time of fixed dose combination AML-B (5 mg) and SIM (10 mg) after a single oral administration in dogs (n = 6).

Conclusion

The individual tablets of amlodipine besylate and simvastatin for continuous release and delayed release of drug respectively has successfully developed and optimized. The optimized formulations are then combined to obtain a differential release of two drugs from a single tablet which is successfully achieved. Amlodipine besylate shows absorption immediately and simvastatin withholds release for close to the desired time of eight h after the administration of the fixed dose combination. The pharmacokinetic parameters, such as the area under the curve, peak plasma concentration and time to reach the peak concentration demonstrate that the drug could be suitable for administration to humans, but with cation until after a pharmacokinetic study in humans confirms the benefits.

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