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REVIEW ARTICLE ON SUSTAINED RELEASE DELIVERY SYSTEM OF ANTI-PLATELET DRUGS

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ABSTRACT

In this article, we have studied about Antiplatelet medications and have seen how Antiplatelet medications works and which drugs are available in the market. Antiplatelet medications currently on the market interfere with one or more phases in the platelet release and aggregation process, leading to a meaningful decrease in thrombosis risk that cannot be separated from an elevated risk of bleeding. Understanding that under physiological conditions, platelets are created daily a quantity that can rise up to 10-fold during times of greater need is crucial when thinking about antiplatelet medications. The maximal circulating life of platelets, is achieved by the fragmentation of bone marrow mega karyocyte cytoplasm.

Keywords: Sustained Release, Antiplatelet medications antiplatelet therapy, oral drug delivery system

INTRODUCTION

Any drug delivery system's primary goal is to deliver a sufficient amount of a medication to an appropriate area of the body so that the necessary drug concentration may be quickly obtained and then sustained. The medication delivery system should release a medicine at a pace determined by the body's needs for a specific amount of time. Regarding these current issues, the distribution method has two crucial components, namely geographical placement and temporal delivery. However, some individuals may be resistant to or have poor responses to antiplatelet medication, or they may have discontinued or paused their antiplatelet therapy for other reasons. Additionally, there is evidence of a rebound impact in platelet activity following the termination of antiplatelet therapy, which may be linked to an elevated risk of cardiovascular event.An optimal drug delivery system should help in the optimization of medication therapy by delivering the desired quantity to the target place at the right pace. As a result, the DDS should give the medicine at a pace determined by the body's demands during the course of therapy. Because it does not account for site-specific absorption rates throughout the gastrointestinal tract, an oral drug delivery system that provides uniform drug distribution can only partially meet therapeutic and biopharmaceutical demands (GIT)

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As a result, there is a need to design drug delivery systems that release the medicine at the appropriate time, location, and rate. The most popular method of medicine delivery is oral. Drug delivery can occur via a variety of routes, but the oral route is preferable since it allows for flexible dosage form formulation and patient compliance. The simplicity of administration, patient acceptability, precise dosage, cost-effective production process, and typically enhanced shelf-life of the product are factors that contribute to the oral route's popularity.

Siji C *et al* prepared carvedilol sublingual tablets which is an oral antihypertensive agent by direct compression using different super disintegrants like croscarmellose sodium, cross povidone, sodium starch glycolate and the solubility enhanced by solid dispersion method. Prepared tablets evaluated for thickness, uniformity of weight, hardness, friability, wetting time, invitro disintegration time, drug content, and in-vitro drug release. The formulation F7 consist of super disintegrantcroscarmellose sodium 5% and drug polymer in the ratio 1:4 shows the maximum drug release.

Harmanpreetsingh *et al* prepared Rizatriptan sublingual tablets by direct compression method using different bio-adhesivepolymers such as sodium carboxy methyl cellulose, HPMC-K4M and chitosan at various concentration ranging from 0.5-5% w/w along with sodium starch glycolate or cross carmellose sodium as superdisintegrants at different concentration ranging 2-8% w/w. The formulation batches containing 2% w/w chitosan along with 2% w/w sodium starch glycolate or cross carmellose sodium which disintegrate rapidly and slow high dissolution and ex vivo permeation. From this the formulation showed increased the bioavailability and directly enter into the systemic circulation.

Wafa Al Madhagi *et al* prepared glimepiride sublingual tablets gives rapid drug absorption that can be used in emergency. These were prepared by using different superdisintegrants like sodium starch glycolate, cross povidone, crosscarmellose sodium, pre-gelatinized starch, and maize starch. The formulations contain binders like flulac and aerosil with disintegration time 21 seconds give the suitable sublingual tablets.

Saroj Makwana *et al* developed sublingual tablets of nicardipine hydrochloride used for the treatment of angina and it having low bioavailability about 10-40% orally attributed to the hepatic first pass metabolism. The solubility of nicardipine enhanced by carried solid dispersion of drug and beta cyclodextrin complex. The sublingual tablets were prepared direct compression method by using sodium starch glycolate, cross carmellose sodium, cross povidone as super disintegrants. The optimized formulation showed in-vitro disintegration time was 41 seconds and 99.95% drug release within the 8 minutes. Formulation containing 4% cross povidone and 2% PVP K-30 show highest disintegration time and ex-vivo permeation was 96.81% within the 14 minutes.

Bhanja SB *et al* developed a sublingual tablet of Perindopril which is an effective drug in the treatment of hypertension. Perindopril containing tablets were prepared by direct compression method using different ingredients such as Crospovidone, Sodium saccharin, Mannitol, Microcrystalline cellulose, Talc and Magnesium stearate. The tablets were evaluated for physical properties including Hardness, Weight variation, Thickness, Friability, Drug content, Wetting time, Water absorption ratio, Invitro disintegration time, In-vitro dissolution study and also Drug release kinetic study. The Hardness, Weight variation, Thickness, Friability and Drug content of tablets were found to be acceptable according to pharmacopoeial limits. An optimized tablet formulation was found, which provided short wetting time of 45 sec, water absorption ratio of 55 and In-vitro disintegration time of 98 sec. because of the amount of superdisintegranti.e.crospovidone was significantly affected the dependent variables like wetting time, Water absorption ratio and In-vitro disintegration time. The best in-vitro drug release was found to be in optimized formulation i.e.99.88% during the end of 12 min. The in-vitro drug release data of all Perindopril sublingual tablets were subjected to goodness of fit test by linear regression analysis according to Zero

order equation, first order equation, Higuchi's equation and KrosmeyerPeppas equation to ascertain the mechanism of drug release.

Modi Foram P *et al.*,formulated and evaluated fixed dose combination moisture barrier film coated bilayer tablet of artesunate and amodiaquine hydrochloride. The tablets were prepared by dry granulation method for artesunate and wet granulation method for amodiaquine hydrochloride. The formula of amodiaquine hydrochloride was optimized using PVPK-30 as a binder.

Durga Prasad Patnayak *et al*., prepared bilayer tablet formulation of metformin hydrochloride and glimepiride Two different matrix formulations were developed, one matrix layer with hydrophilic swellable polymer and another with hydrophobic polymer as carriers for sustained drug delivery from matrices and were evaluated. Hydroxypropylmethylcellulose and Polyethylene oxide was used as polymers in order to get the sustained release profile over a period of 24 h. Tablet s were evaluated for physical properties; drug content and in vitro drug release were compared with standard commercial tablet s (Glimy-M). The excipient s used in this formulation did not alter physicochemical properties of drug, as tested by HPLC, DSC, and FTIR. Stability of the drug release profiles at 6 months in 40◦C and 75%RH suggesting that HPMC based sustained release formulation was stable than the Polyethylene oxide sustained release formulation due to its stable and better targeting profile in terms of drug release.

Muthukumaran M *et al*., fabricated and evaluated of sustained release mucoadhesive bilayer tablets containing Nifedipine using the Natural Bioadhesive polymers such as Pectin to compare the synthetic polymer like Carbopol 971- P, HPMC-K4M and Polyvinyl pyrrolidone (PVP- K30) along with ethyl cellulose and magnesium stearate as an impermeable backing layer to improve the oral bioavailability. The pre formulation study was performed by FTIR and DSC. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water impermeable agent was compressed on the first layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release. The surface pH of all the tablets was close to neutral pH the mechanism of drug release was found to be non-fickian diffusion.

Mujoriya R Z *et al*., developed and evaluated metoprolol succinate er and amlodipine besilate bilayer tablet by using different polymer (HPMC, Methocel, Carbapol) with different diluents (MCC, Cellulose Phosphate, Starch, Croscarmalose Sodium) and then evaluated. The experimental work was divided into Preformulation studies, formulation development and evaluation. Standardization of drug and excipients confirmed the authentication of the samples. Thus 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. It was found that the in vitro drug release of Metoprolol succinate ER was best explained by first order (r2 =0. 9994), as the plots showed the highest linearity, followed by Higuchi's equation (r2 = 0.9974) and zero-order (r2 = 0.9471).

Akash Yadav *et al.*, developed a bilayer and Floating-Bioadhesive drug delivery system exhibiting a unique combination of floatation and bio adhesion to prolong residence in the stomach using propranolol hydrochloride 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. 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 from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied. 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. This kind of tablet exhibits independent regulation of buoyancy and drug release.

Jain Jitendra *et al.*, was developed a bilayer-floating tablet (BFT) for Indomethacin using direct compression technology. Bilayer tablets were punched using optimized solid dispersion, HPMC K4M, Avicel PH-112, ac-di-sol, magnesium stearate and aerosil in fast release layer and optimized floating layer as sustained release layer. Tablets were evaluated for physic -Chemical properties such as Hardness, Friability, Thickness, weight Variation and drug content uniformity. FT-IR studies are performed. In Vitro dissolution studies were carried out in a USP type II Paddle type apparatus. The optimized formulation (A2) showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60ºc/80% RH for 3 months. The release data obtained from the dissolution study of the bilayer tablets were analyzed with respect to first order model, Higuchi model, Korsmeyer-Peppas model, and zero order models. In this study optimized formulation (A2) release the drug up to 24hrs.

Ajit Kulkarni *et al.*, prepared the regio-selective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile by direct compression technique. The bilayer floating tablets comprised of two layers, immediate release layer of sodium starch glycolate as a super disintegrant and the sustained release layer comprised of Hydroxy propyl methyl cellulose (HPMC) K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All formulations formulated for more than 12 hours and released 90% of lovastatin within 30 min. Roentgenography was carried out to study the in vivo buoyancy of the optimized formulation and it was found to be buoyant for 8 hour in stomach.

Ziyaurrahman *et al.*, developed the bilayer- floating tablets of captopril using direct compression method. The floating layer was formulated with HPMC K- grade (K4M, K15M and K100M) and effervescent mixture of citric acid and sodium bicarbonate. The sustained release layer comprised of captopril and various polymers such as HPMC- K15M, PVP-K30 and Carbopol 934p alone or in combination with the drug. Final formulation released approximately 95% of drug in 24 hours in vitro, while the floating lag time was 10 min and the tablet remained floatable throughout the studies. Placebo formulation containing barium sulphate in the release layer administered to human volunteers for in vivo X – ray studies showed that BFT had significantly increased the gastric residence time.

Abdul Althaf S *et al.*, formulated and evaluated the bilayer immediate release tablets of clopidogrel biphosphate and aspirin. This study was intended to produce an immediate release bilayer tablet using solid dispersion technique. The prepared tablets were evaluated for the dissolution. The dissolution followed zero order kinetics as it is independent of concentration. Fusion method was employed for preparing solid dispersion as it improves safety and efficacy, and intern improves its bioavailability. Formulations F2, F3, F4 were taken to study the effect of super disintegrants like sodium starch glycolate, crospovidone, Croscarmalose sodium respectively. 6% super disintegrants concentration showed better release profile compared with other concentrations.

Kotta kranthi kumar *et al* formulated and evaluated bilayered tablets containing Pioglitazone hydrochloride for immediate release using cross Povidone as super disintegrant and Metformin hydrochloride for sustained release using polyethylene oxide (PEO-303) as matrix forming polymer. The tablets were evaluated for physicochemical properties. All the values are found to be satisfactory. In-vitro release studies were carried out as per USP in pH 1.2 and phosphate buffer pH 6.8 using the USP apparatus II. The release kinetics of Metformin hydrochloride was evaluated using the regression coefficient analysis. The formulated tablets (F5) shows first order release and diffusion was the dominant mechanism of drug release. The polymer Polyethylene oxide (PEO- 303) had significant effect on the release of Metformin HCl matrix tablets (F5). Thus, formulated bilayer tablets proved immediate release of Pioglitazone and

Metformin HCl as sustained release over a period of 12 hours. The stability studies and FT-IR studies were also indicating the absence of strong interactions between the components and suggesting drug-excipient compatibility in all the formulations examined.

Arunachalam.a *et al.*,prepared levofloxacin hemihydrate floating tablets by melt granulation method using the polymer, hydroxy propyl methyl cellulose (HPMC K100M) with different amounts and other excipients and sodium bicarbonate as gas generating agent. They developed a floatable drug delivery system of Levofloxacin hemihydrate for sustained drug delivery and gastric retentive property with special emphasis on optimization of formulations for floating matrix tablets. Levofloxacin floating tablet drug delivery system showed improved in-vitro bioavailability and extended drug release which may favour the reduced dose frequency and patient compliance.

Shafayad Hossain Md *et al*. develop a formulation of Ticagrelor 90 mg tablets that is equivalent to the reference product using similar excipients to match the in-vitro dissolution profile. A compressed coated tablet was formulated consisting of Ticagrelor and excipients conforming to the USP/BP monograph and below maximum amount allowed per unit dose. The physical characteristics of powder blends were evaluated. The compressed core and coated tablets were evaluated for thickness, hardness, weight variation, friability, disintegration, dissolution, drug content.

Dobesh PP *et al.*, Inhibiting the P2Y12 platelet receptor has demonstrated an ability to reduce adverse CV outcomes significantly over the use of aspirin alone. Despite over a decade of use with clopidogrel, the agent has a number of limitations that need to be addressed. Ticagrelor is a P2Y12-receptor inhibitor that overcomes many of these limitations. The different chemical structure, which is not a prodrug, allows for rapid, potent, and consistent inhibition of platelet aggregation. These attractive pharmacologic, pharmacokinetic, and pharmacodynamic properties may have contributed to a significant reduction in thrombotic events in the phase III PLATO trial.

Teng *et al.*, The non-P2Y12 receptor actions of Ticagrelor warrant further investigation, in particular the possible beneficial effects on cardiac perfusion. Current data suggest that, if necessary, patients who are not responsive to clopidogrel can be switched directly to Ticagrelor with an increase in IPA. In contrast, switching from Ticagrelor to clopidogrel is associated with a reduction in IPA. Genetic variations appear to influence response to clopidogrel. However, there is currently no evidence to show that this is true for Ticagrelor. Ongoing studies will provide additional insights into the pharmacology of Ticagrelor and will help support individualized P2Y12 inhibitor treatment, in line with guideline recommendations.

Fuller R *et al.*, Ticagrelor offers a treatment option for patients with ACS and is included in the American Heart Association/American College of Cardiology 2011 guidelines for secondary prevention and risk-reduction therapy for patients with coronary and other atherosclerotic vascular diseases. In the pivotal PLATO trial, Ticagrelor treatment significantly reduced mortality rates from vascular causes, nonfatal MI, and stroke compared with clopidogrel, but it was associated with a significant increase in the rate of non–procedure-related bleeding.4,6 Ticagrelor also showed higher rates of dyspnea, intracranial bleeding, and premature discontinuations resulting from adverse events.The increased cost of Ticagrelor, compared with that of competitor drugs, as well as the need for twice-daily dosing (compared with once-daily for competitors), are also important considerations in formulary decision-making.

Lee D *et al.*, The SR formulation of Cilostazol was not significantly different in AUC compared with that of the IR formulation, although it did display a significantly lower C(max) per dose in both the single- and multiple-dose groups. Food significantly increased the bioavailability of the SR formulation. The Cilostazol SR and IR formulations were well tolerated in all parts of the study, with no serious adverse events reported.

Hoshino H *et al.*, The combination of Cilostazol and Clopidogrel significantly reduced the recurrence of ischemic stroke without increasing the bleeding risk in noncardioembolic, high-risk patients.

Elam *et al.*, The phosphodiesterase inhibitor Cilostazol also favourably modifies plasma lipoproteins. Specifically, plasma levels of HDL-C and apoA1 are significantly increased and plasma triglycerides are decreased. Both the triglyceridelowering and HDL-raising effects of Cilostazol are more pronounced in individuals with baseline hypertriglyceridemia. The observed beneficial lipoprotein-modifying effect of Cilostazol, in addition to its previously reported antiplatelet properties, offers the possibility that long-term therapy with this agent will not only alleviate the symptoms of IC but may also favorably alter the clinical course of atherosclerotic peripheral vascular disease. This remains to be determined and will require long-term study of the effects of Cilostazol.

Sorkin *et al.*, Cilostazol has been well tolerated, with the most common adverse events being headache, diarrhoea, abnormal stools and dizziness.In a 24-week randomised double-blind trial in patients with intermittent claudication, Cilostazol 100mg twice daily produced significant improvements in pain-free and maximum walking distances, compared with pentoxifylline (oxpentifylline) 400mg 3 times daily and placebo.

Dawson DL *et al.*, Cilostazol is an agent with pharmacological actions unlike other drugs used for the treatment of chronic occlusive arterial disease. This study represents a preliminary examination of its efficacy for treatment of the symptoms of intermittent claudication. Although this limited trial showed a statistically significant improvement in treadmill walking performance after 12 weeks of therapy with Cilostazol 100 mg PO BID, and patients' subjective assessment of symptoms corroborated this finding, additional studies with larger numbers of participating claudication patients are needed to confirm efficacy. The positive results of the current study are encouraging, and larger trials have been initiated to answer some of these questions.

Chi YW *et al.*, Cilostazol remains the only drug thus far proven to demonstrate consistent benefits in clinical trials in patients with IC. In addition to limb-specific outcomes, Cilostazol has also been shown to provide pleotropic effects; these may provide additional clinical benefits, but clinical trials are needed to validate such effects. Finally, studies are also needed to compare the effects of Cilostazol and supervised exercise training in patients with IC to either therapy by itself.

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