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Trimetazidine 80 mg once daily: a novel formulation developed with Multi-layer MicrogranularTechnology (MLMT) and its clinical benefits

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ABSTRACT: Trimetazidine is an effective, well tolerated antianginal anti-ischemic agent. Due to shorter plasma half-life, it is prescribed as 20 mg tablets given thrice daily (TID) to ensure relatively constant plasma levels. However, to overcome multiple administrations, its modified-release (MR) formulation is also available in the market as compressed matrix tablets administered as 35 mg twice daily (BID) that provide corresponding drug release up to 12 h. Recently, a new formulation of trimetazidine 80 mg once daily (OD) extended release capsules has been developed with a unique multi-layer microgranular technology (MLMT), which allows once-a-day dosage regimen with drug release up to 24 h with an aim to simplify treatment for better patient adherence ultimately translating into better angina control. These capsules developed with MLMT is approved in 42 countries and are now available in India as Flavedon OD 80 mg capsules. In this review, we summarize the unique technology (MLMT) used in the development of trimetazidine 80 mg OD and its clinical benefits in the management of patients with coronary artery disease. Many generic MR formulations of trimetazidine (35 mg and 60 mg oral tablets/capsules) are also available in India.

KEYWORDS: Capsules; patient compliance; MLMT; Trimetazidine

I. INTRODUCTION

Despite wide availability of medical treatments offering alleviation from angina symptoms,[1] management of angina has been reportedly sub-optimal.[2-5] Among factors that contribute towards sub-optimal angina control, treatment non-adherence is well known in about 50% of patients with cardiovascular diseases (CVD) including coronary artery disease (CAD).[6-8] Treatment non-adherence associates with several factors[8,9] and reportedly relates to the number of medications and the number of doses per day but is inversely associated with the latter.[10,11] Patient compliance is mostly a part of the success story of many drug products in the market.[12] Oral modified-release (MR) formulations are widely used to improve patient compliance by reducing the dosing frequency.[12] The MR delivery systems may help achieve desired plasma drug concentration and maintain the same for longer periods compared to immediate-release (IR) formulations.[12] Benefits of oral MR formulations have been utilized and well-studied.[13] Common oral MR formulations include, but are not limited to, soluble matrix, insoluble matrix, coated beads, coated tablets, tablets or beads, osmotic pump tablets, combinations of different MR formulation designs, and its combination with IR formulation design.[12] However, development of MR oral formulation from drug characteristics until the end-usage results of clinical benefits is a challenge; and advanced technology plays a unique role in its development process.[14, 15]

Trimetazidine is an effective and well tolerated antianginal drug with protective actions against ischemia-induced heart injury.[16] Trimetazidine is used in the long-term treatment of angina pectoris. Its mechanism and clinical efficacy for various cardiac continuums have been elaborated elsewhere.[16] Trimetazidine is a piperazine derivative and a poorly soluble drug therefore, is used as freely water-soluble trimetazidine hydrochloride salts.[16] Trimetazidine is administered orally in divided doses as an IR preparation. It is quickly absorbed and eliminated, and has a plasma half-life of around 6.0+/-1.4 h and a T_{max} of around 1.8+/-0.7 h. Owing to its shorter plasma half-life, in routine practice, 20 mg preparation is given thrice daily (TID) to ensure relatively constant plasma levels.[17] However, to overcome multiple daily administration challenges, MR formulation of trimetazidine is also available in

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the market as compressed matrix tablets administered orally as 35 mg twice daily (BID) that provide drug release for up to 12h.[17,18] Recently, newer formulation of trimetazidine 80 mg allowing dosage regimen OD was developed as capsules with a unique Multi-layer MicrogranularTechnology (MLMT) by Les Laboratories Servier, France with the aim to simplify treatments thus, providing an opportunity to increase patient adherence in addition to clinical benefits similar to previous trimetazidine dosages. Many generic MR formulations of trimetazidine administered as 35 mg and 60 mg oral tablets are also available in India. We summarize the unique technology (MLMT) used for development of trimetazidine 80 mg OD capsules and their clinical benefits in this review.

II. NOVEL MLMT IN THE DEVELOPMENT OF TRIMETAZIDINE 80 MG OD

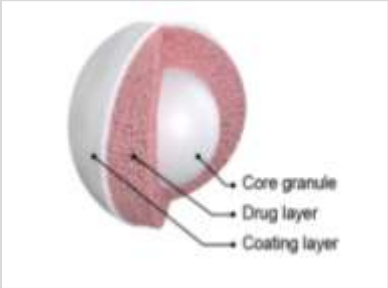

Figure 1 Multi-layer microgranule

Oral MR drug delivery system includes either single- or multiple-unit dosage forms, the latter consisting of pellets/beads/microgranules, microparticles and minitablets. Multiple-unit dosage forms have several advantages:[14,19]

- Spreads uniformly in the gastrointestinal tract thus, reduces local irritation, enhances drug absorption and lowers fluctuation of drug release and drug peak in plasma
- Possesses constant transit time to avoid dose-dumping and improves safety
- Any defect in case of individual unit has no effect on efficacy
- Inter-and intra-individual bioavailability variations of fed conditions can be reduced

Among multiple-unit dosage forms, pellets/beads/microgranules are globular and can be coated for the MR of the drug. To act as an effective MR dosage form, microgranules are coated with a polymer that are then either compressed into tablets or filled into hard gelatin capsules as the final dosage form (Figure 1).[20]

During formulation process of tablets, compression force exerted on coated microgranules often damages the polymer coating and subsequently leads to dose-dumping and rapid drug release. On the other hand, the novel trimetazidine 80 mg OD formulation is a capsule formulation that offers two main advantages. First, in the absence of compression forces, the coating on microgranules remains intact resulting in uniform drug release. Secondly, it reduces the amount of release control polymer required to get 24 h release profile for higher dose (80 mg) of trimetazidine. In fact, to get a 24 h release profile of trimetazidine 80 mg in tablets, higher quantities of release control polymers are required that might increase the tablet size and cause swallowing difficulties leading to non-compliance. Coated microgranules of trimetazidine in capsules offer the advantage of uniform drug release at the size of capsules almost equivalent to that of 35 mg BID tablet may improve patient compliance.

III. PROCEDURAL STEPS FOR MLMT OF TRIMETAZIDINE 80 MG OD CAPSULE FORMULATION

In the development of trimetazidine 80 mg OD capsule containing multi-layer microgranules, uniform coating of the drug layer and the polymer layer over the pellet core is a challenge considering the freely soluble nature of trimetazidine hydrochloride. To overcome these, fluidized bed coater –Wurster coater (bottom spraying process) is utilized to optimize both layers over the core pellets for maintaining uniform drug-release profile of first-order kinetics throughout 24 h.[15] The schematic

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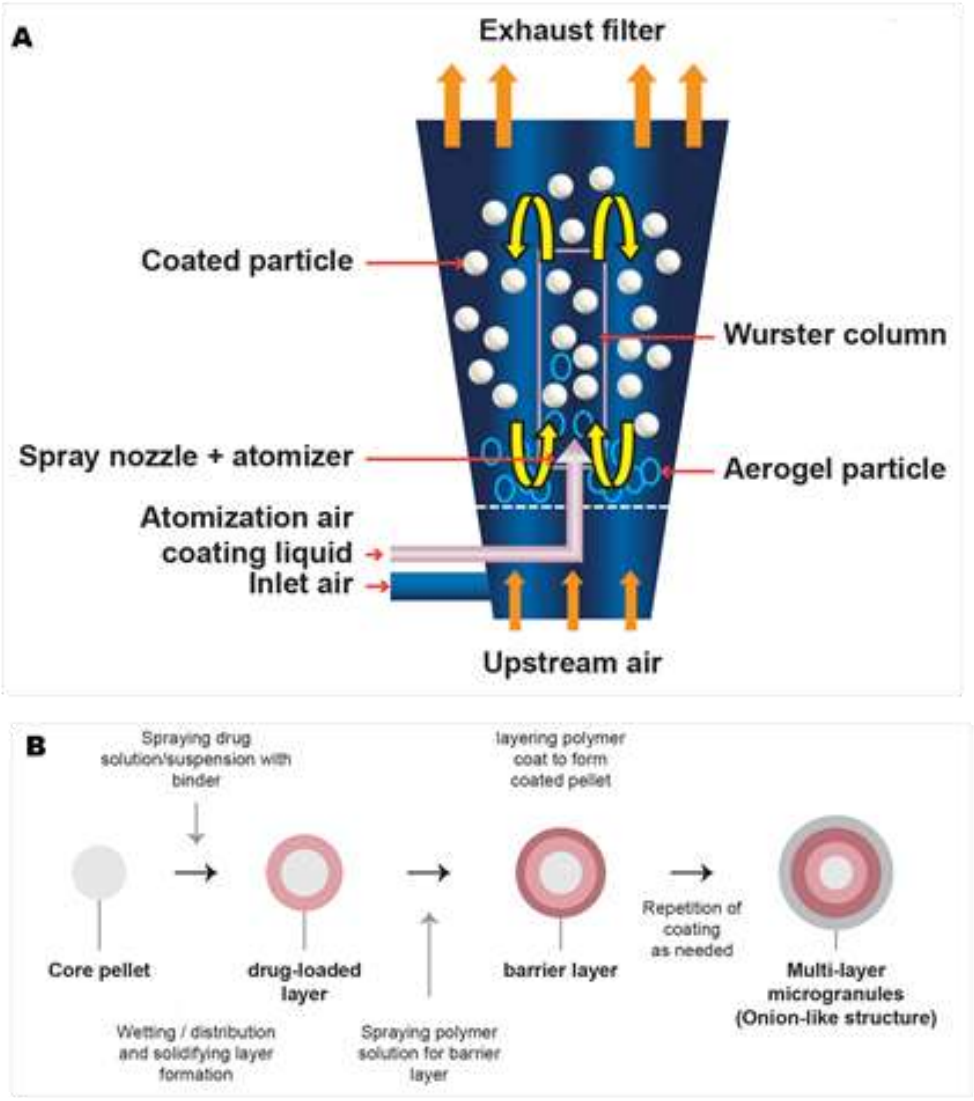

Figure 2 Schematic representation of process of coating in Wurster coater (A) and mechanism of coating to form multi-layer microgranules (B)

representation of coating process in a Wurster coater (A), and the mechanism of coating to form multi-layer microgranules (B) are given in the Figure 2.

The Wurster coating process was invented about 30 years ago and evolved through elaborate design modifications and refinement into an ideal equipment for pellet manufacturing by solution/suspension layering.[21] High drying efficiency inherent in fluid bed equipment coupled with innovative and efficient design features of the Wurster process allows the machines to hold a stand in pharmaceutical processing technology. However, inaccessibility of the nozzle is one of its disadvantages. If the nozzles are clogged during the layering process, operation must be interrupted and the spray guns must be removed for cleaning. This problem can be alleviated by screening the formulation or by using a spray gun with a bigger nozzle. Another challenging aspect is using multiple nozzles that can lead to potential overlap of adjacent spray zones. Although the position of the nozzle is fixed, the spray zone overlap can be minimized using the air cap at the end of the spray gun.

For processing, all components of the formulations are first dissolved or suspended in a medium to provide optimal formulation of the

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desired viscosity that is sprayed over fluidized pellet bed.[21] The sprayed droplets immediately impinge on the started seeds and spread evenly on the surface, provided the drying conditions and fluid dynamics are favourable.[21] Following this is a drying phase that leads to precipitation of dissolved materials forming solid bridges holding the formulation components tighter in the form of successive layers on the core pellet/microgranule.[15, 21] The process continues until the desired quantity of drug substance and the target potency of the pellets is achieved. Ideally, no new nuclei are formed, and the particle population remains the same.[21] However, the size of microgranules increase as a function of time and as a result, the total mass of the system also increases. However, optimization of process variables is difficult for the successful development of a pelletized product. Moreover, to avoid delamination or damage of the drug layer over the core during subsequent layering and drying processes, binders of polymers are used that impart strength to the microgranules.[21] Although it is possible to manufacture microgranules from a formulation that does not contain binders, almost invariably, layers of the drug applied tends to delaminate or break off from the cores in the later stages of the layering process or in the subsequent drying step. Therefore, binders are consistently used during this process to impart strength to the microgranules. They are usually low-molecular-weight polymers that are compatible with the drug substance. Similarly, for trimetazidine 80 mg OD capsules containing multi-layer microgranules, cores of microgranules were coated with successive layers of the trimetazidine using fluidized-bed apparatus-Wurster coater.[15]Drug and the binder coated the innermost layer over the neutral core microgranule whereas, the release control polymer (cellulose derivatives and plasticizers) coated the outer layer. The solution/suspension of trimetazidine and the binder was sprayed onto the cores from the inlet present at the bottom of coater and was dried followed by successive layering of drug-release retardant solution/suspension.[22] This release retardant is responsible for diffusion of trimetazidine and thus, controls the drug release kinetics for 24 h. The coated dried pellets/microgranules/beads were lubricated and filled in suitable-sized capsules as the finished dosage form.[22]

The in vitro dissolution of trimetazidine 60 mg formulations tablet/capsules showed dose-dumping in the first 4 h and released the active drug (70%) for only up to 12 h. Moreover, at the end of 8 h, super-saturation was seen in the dissolution media with complete drug release thus, the absolute drug release from the end of 8 h to 24 h was negligible (≤3%). The in vitro dissolution of trimetazidine 80 mg OD showed that 20.9% of the drug released by 4 h; 48.5%, by 8 h; and 86.3%, by 24 h.[22]Trimetazidine 80 mg OD provided gradual and sustained drug release over 24 hresulting in therapeutically efficacious plasma levels (≥40µg/L)obtained in a prolonged manner over 24 h following its oral administration. Moreover, its therapeutic concentration was achieved within ~3 h.[22]The drug-release profile showed that the microgranules containing capsules provided drug release over 24 h without bursting or dose-dumpingor discontinuation.[22] Uniform drug release from trimetazidine 80 mg OD was obtained owing to micropore formation in the coated membrane layer of microgranules that diffuses the drug via first-order drug release mechanism (diffusion of drug from micropores and erosion of polymer). Overall, this novel formulation provided invitro release profile for 24 h. Moreover, the data from pharmacokinetic and bioavailability studies provided equivalence bioavailability and pharmacokinetic profile of the product to that of trimetazidine 35 mg BID.

IV. CLINICALBENEFITSOFTRIMETAZIDINE 80 MG OD FORMULATION

Amulti-layer microgranular formulation of trimetazidine 80 mg OD, owing to its OD dosage and similar drug release profile, can improve patient compliance and clinical benefits. Studies have shown that long-acting trimetazidine 80 mg OD could be effective and well tolerated in treating patients with chronic angina.[23-25] Trimetazidine OD 80 mg capsules developed by MLMT (approved in 42 countries) is now available and approved as Flavedon OD 80 mg in India by the drug authorities. It is patented globally as well as in India under Indian Patent no. 305171. A step towards success of any formulation is in its clinical acceptability.Pozdnyakov et al. assessed the clinical acceptability of trimetazidine 80 mg OD formulation compared to trimetazidine MR 35 mg BID in an international multi-center phase III study in patients (N=165) with previously diagnosed stable angina.[23] Results showed similar safety profiles of trimetazidine 80 mg OD and trimetazidine 35 mg BID and thus, could improve patient compliance and provide clinical benefits.[23] Subsequently, ODA (antianginal effectiveness and tolerability of trimetazidine modified release 80 mg

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Once Daily instable angina patients in real-world practice), a real-world study by Glezer et al. in Russian patients (N=3066) with stable angina and persistent symptoms despite therapy reported that patients treated with trimetazidine OD for 3 months had reduced number of angina attacks and nitroglycerin use, and improved physical activity and treatment adherence.[24] The study also reported that this new OD formulation of trimetazidine could provide an opportunity to improve patients' angina symptoms and encourage them to follow their treatment. Glezer et al. also assessed efficacy of long-acting trimetazidine in different clinical situations in patients with angina from the ODA trial.[25] The results showed that this formulation, in association with other antianginal therapy, was found to be effective and well tolerated in patients initiating trimetazidine treatment and in those switching from BID or TID formulation of trimetazidine.[25] We believe that trimetazidine 80 mg OD capsules formulated by MLMT, owing to its 24 h drug release profile and bioequivalence to trimetazidine 35 mg BID, could offer similar efficacy and safety in patients with angina.

V. SUMMARY

Trimetazidine is an effective and well-tolerated treatment option for patients with angina pectoris. Available IR and controlled dosage forms of trimetazidine require multiple daily dosing. Novel trimetazidine 80 mg OD capsule formulation developed using MLMT has the advantage of uniform drug release over 24 h, and was found bioequivalent to trimetazidine 35 mg BID in pharmacokinetic studies. This novel trimetazidine 80 mg capsule prepared using MLMT requiring OD administration may overcome the challenge of poor adherence and can offer optimal clinical benefits.

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