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A novel co-processed directly compressible release-retarding polymer: In vitro, solid state and in vivo evaluation

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ABSTRACT

Directly compressible (DC) co-processed excipient capable of providing nearly zero order release with improved functionality was developed without any chemical modification by employed various techniques such as physical mixing, high shear mixer granulation and spray drying. Co-processed excipient was developed by using release retarding polymer Eudragit RSPO, separately, in combination with different concentration of hydroxyl propyl methyl cellulose 100 cps (Methocel K100 LV, HPMC), ethyl cellulose (Ethocel N50, EC) and hydroxyl propyl cellulose (Klucel EF, HPC). All co-processed excipients were evaluated for their flow properties in terms of angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. Out of eighteen combinations, the nine co-processed excipients exhibited promising flow properties were found suitable for direct compression and formulated as tablets. Metoprolol succinate, a BCS Class I drug, was selected as a model drug and the formulation was developed employing direct compression approach. The developed tablets were evaluated for physical parameters like uniformity of weight, thickness, hardness, friability and assay. *In vitro* dissolution study confirms that formulation prepared using co-processed excipient showed sustained drug release. The optimized tablet formulation was characterized by DSC, FTIR and PXRD which confirms the absence of any chemical change during co-processing. The optimized formulation was kept for stability study for six months as per ICH guidelines and found to be stable. *In vivo* pharmacokinetic study of optimized formulation in rats showed similar pharmacokinetic behaviour as was observed with the marketed brand. Study revealed that co-processed excipient has advantage over polymers with single property and can be utilised for sustained release formulation.

1. Introduction

Owing to busy and sedentary lifestyle these days, people are affected by a number of lifestyle diseases [1]. Majority of these require prolonged treatments leading multiple drug dosing within a day. Thus, numerous research has been done on controlled release products and technologies for a wide variety of drugs [2–4]. Still, achieving a perfect zero-order release has always remained a goal-post. Today, such a release profile is achievable only with advanced technologies like osmotically controlled drug delivery systems sometimes using laser drilling technology [5–7]. The other options of polymers do not offer such advantages because majority of the cellulose-based polymers are swellable in nature [8,9]. The initial swelling results in loss of geometry of dosage form, thus resulting in release profiles following Higuchi or Korsemeyer-Peppas models. Hydrophobic polymers like ethyl cellulose [10] and non-polar grades of Eudragits [11] are also employed for control of release of drugs. However, these polymers are mostly employed as additional coating materials owing to their inability to form matrices. Moreover, majority of these coatings employ non-aqueous solvents which is an environmental hazard too.

Waxy matrices such as carnauba wax [12], bees wax [13], glyceryl behenate [14] are non-swellable in nature and provide good release retardation but these polymers are also not able to provide a zero-order release. This is because the most common mechanism of drug release from waxy matrices is diffusion. Another problem associated with waxy matrices is the change in dissolution performance upon long term storage. Also, there are processability

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issues like sticking associated with these polymers particularly while using high speed machines.

Several co-processed excipients for immediate release formulation are available on the market e.g. Ludipress, Cellactose etc. The improved manufacturing efficiency and reduced cost of the final drug product can be obtained by using the co-processed excipient. But there is no commercially available co-processed excipient for sustained release matrix formulation.

Novel co-processed excipients can also be employed in oral sustained release dosage forms which deliver the drug for longer period and helps in producing the therapeutic effect for 24 h for those drugs which are having low plasma half-life.

Metoprolol Succinate, *((±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1)*, having molecular formula $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ is a white crystalline powder and freely soluble in water. The oral bioavailability of metoprolol is 50–70% and it has very low plasma half-life 2–5 h. Metoprolol succinate, β1-selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4–6 h and in normal course of therapy, frequent drug administration is required every 4–6 h, thus need the use of sustained release formulation for prolong action and to improve patient compliance by utilizing co-processed excipients.

In our study, we have developed a co-processed sustained release excipient utilizing a synthetic polymer and other filler via various preparation methods. This co-processed excipient is designed to be used for directly compressed sustained release matrix formulation, which can give near zero order release.

Hence, the objective of the current research was to develop a co-processed excipient which can be employed as directly compressible excipient, with minimum adjuncts, to provide a nearly zero-order release of highly soluble BCS Class I model drug (metoprolol succinate). For the purpose it was envisaged to co-process a non-polar, non-swellable methacrylic acid based excipient, Eudragit RSPO (containing about 5% hydrophilic amine group) with other swellable and non-swellable excipients in order to obtain a novel co-processed excipient.

2. Materials

Eudragit RSPO was purchased from M/s Evonik Industries, Mumbai, India. Metoprolol succinate was received as a gift sample from M/s Lupin Ltd., Pune, India. Hydroxypropyl methyl cellulose 100 cps (Methocel K100 LV, HPMC) and Ethyl cellulose (Ethocel N50, EC) were obtained from M/s Colorcon India, Goa. Hydroxypropyl cellulose (Klucel EF, HPC) was procured form M/s Ashland, Mumbai, India. All other reagents, chemicals and solutions used were of analytical grade.

3. Methods

3.1. Preparation of co-processed polymers

For co-processing, a non-swellable polymer, Eudragit RSPO (Eudragit) was co-processed with three different polymers, viz. hydroxypropyl methyl cellulose 100 cps (Methocel K100 LV, HPMC), ethyl cellulose (Ethocel N50, EC) and hydroxypropyl cellulose (Klucel EF, HPC). Colloidal silicon dioxide (Aerosil 200 Pharm) was added to enhance the flow the polymer blend. The various methods utilised for co-processed polymers are as follows:

3.1.1. Physical mixing

Eudragit was physically mixed with the three polymers as per Table 1. Colloidal silicon dioxide was added in a concentration of 0.5% in the polymer mixtures to obtain co-processed polymers, PM-1 to PM-6.

3.1.2. High shear mixer granulation

The excipients combinations as depicted in Table 2 were subjected to high shear granulation. Briefly, each individual polymer mixture along with 0.5% colloidal silicon dioxide was transferred to the bowl of high shear mixer and granulator (M/s Kevin, Ahmedabad, HSMG) and was thoroughly mixed for 10 min at an impeller speed of 150 rpm. The mixed polymers were granulated with a 1:1 mixture of isopropyl alcohol (IPA) and dichloromethane (DCM) employing impeller at a speed of 150 rpm for first 2 min followed addition of chopper mixing at 1500 rpm for additional 1 min. The kneading was repeated till the granulation end-point (2.3 AMP) was achieved. The wet mass was passed through 2 mm screen fitted at the outlet of HSMG. The wet granules were dried in a fluidized bed drier at temperature of 60 °C till an LOD of less than 2% w/w was achieved. The dried granules were milled through 40 G screen fitted in a co-mill at a speed of 4000 rpm to obtain co-processed polymers HG-1 to HG-6.

3.1.3. Spray drying

Polymer combinations as depicted in Table 3 were employed for the purpose of spray drying. Eudragit was dissolved in a 1:1 mixture of acetone and IPA. The other polymer was dissolved in a 1:1 mixture of IPA and DCM. Both the solutions were mixed and colloidal silicon dioxide was added in a concentration of 0.5% w/w. The resultant mixture was kept under stirring and spray dried at an inlet temperature of 35 ± 3 °C with an atomization pressure of 0.9 ± 0.1 bar and an air flow of 40–60 cfm to obtain co-processed polymers SD-1 to SD-6.

3.2. Evaluation of co-processed polymers

3.2.1. Angle of repose

The angle of repose was determined by the funnel method. The determination of angle of repose by this method is referred to as static angle of repose. Powder is poured onto the centre of the dish from the funnel that can be raised vertically until the maximum cone height (h) is obtained. The angle of repose can be calculated by the given formula,

$$\alpha = \tan^{-1}(h/r)$$

where 'h' is height of pile and 'r' is radius of pile (As per USP method). The flow properties and corresponding angle of repose are given in Table 4.

3.2.2. Bulk density (BD)

Bulk density of various co-processed excipients was determined by USP bulk density apparatus (Electrolab). It was measured by

Table 1
Physical mixtures of excipients.

Excipients mixture	Ingredients	Ratio
PM-1	Eudragit: HPMC	1: 0.5
PM-2	Eudragit: HPMC	1: 0.75
PM-3	Eudragit: EC	1: 0.25
PM-4	Eudragit: EC	1: 0.5
PM-5	Eudragit: HPC	1: 0.5
PM-6	Eudragit: HPC	1: 0.75

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