List of Publications

Research publications

1) **Riddhish Patadia**, Chintan Vora, Karan Mittal, Rajashree Mashru. Investigating critical effects of variegated lubricants, glidants and hydrophilic additives on lag time of press coated ethylcellulose tablets. ***Pharmaceutical Development and Technology*** 2016; 21(3): 302-310.

2) **Riddhish Patadia**, Chintan Vora, Karan Mittal, Rajashree Mashru. Investigating effects of hydroxypropyl methylcellulose (HPMC) molecular weight grades on lag time of press coated ethylcellulose tablets. ***Pharmaceutical Development and Technology*** 2015; Early online: 1-9. [DOI: 10.3109/10837450.2015.1055767].

3) **Riddhish Patadia**, Chintan Vora, Karan Mittal, Rajashree Mashru. Quality by design empowered development and optimization of time-controlled pulsatile release platform formulation employing compression coating technology. ***AAPS PharmSciTech*** 2016; Early online: 1-15. [DOI: 10.1208/s12249-016-0590-3].

Review publication

1) **Riddhish Patadia**, Chintan Vora, Karan Mittal, Rajashree Mashru. Dissolution criticality in developing solid oral formulations: From inception to perception. ***Critical Reviews^{TM} in Therapeutic Drug Carrier Systems*** 2013; 30(6): 495-534.

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RESEARCH ARTICLE

Investigating critical effects of variegated lubricants, glidants and hydrophilic additives on lag time of press coated ethylcellulose tablets

Riddhish Patadia, Chintan Vora, Karan Mittal, and Rajashree Mashru

Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Vadodara, Gujarat, India

Abstract

The research envisaged focuses on vital impacts of variegated lubricants, glidants and hydrophilic additives on lag time of press coated ethylcellulose (EC) tablets using prednisone as a model drug. Several lubricants and glidants such as magnesium stearate, colloidal SiO_2, sodium stearyl fumarate, talc, stearic acid, polyethylene glycol (6000) and glyceryl behenate were investigated to understand their effects on lag time by changing their concentrations in outer coat. Further, the effects of hydrophilic additives on lag time were examined for hydroxypropylmethylcellulose (E5), hydroxypropylcellulose (EF and SSL), povidone (K30), copovidone, polyethylene glycol (4000), lactose and mannitol. *In vitro* drug release testing revealed that each selected lubricant/glidant, if present even at concentration of 0.25% w/w, significantly reduced the lag time of press coated tablets. Specifically, colloidal SiO_2 and/or magnesium stearate were detrimental while other lubricants/glidants were relatively less injurious. Among hydrophilic additives, freely water soluble fillers had utmost influence in lag time, whereas, comparatively less impact was observed with polymeric binders. Concisely, glidant and lubricant should be chosen to have minimal impact on lag time and further judicious selection of hydrophilic additives should be exercised for modulating lag time of pulsatile release formulations.

Keywords

Chronotherapeutic, compression coating, excipient, pulsatile release formulation

History

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Introduction

Now-a-days, the growth of compression/press coating technology is steadily intensifying in the field of pulsatile release (PR) or delayed release (DR) formulations. The technology offers several advantages like isolation of incompatible ingredients, protection of light/acid/moisture sensitive drugs, continuous and solvent-less processing, etc. The technology can be efficiently employed in designing of chronotherapeutic drug delivery systems to target drug release at specific site or predetermined time[1–4]. In chronological disorders such as rheumatoid arthritis, asthma, angina pectoris, hypertension, etc. the circadian rhythm of the body provokes early morning disturbances when patients are asleep[1,2,5]. The conventional way of treatment is to deliver a higher dose of drug in either form of immediate release (IR) or sustained release (SR) formulations before going to bed so as to maintain the therapeutic concentration till the next morning. This approach of delivering a higher dose of drug is rather inappropriate as it continuously causes side effects and imparts metabolic load on the body even when the effect is not actually required. On the contrary, PR formulations which can specifically target the drug release only at early morning would be more beneficial[1,4]. Such PR formulations demonstrate specific lag time during which the drug release is restricted followed by burst release. The lag time of a PR formulation is to be designed according to drug pharmacokinetics and disease requirement. In the treatment of early morning attacks with chronological disorders, 4–6 h of lag time is desired if time to show peak effect is approximately 1–3 h. Administration of such formulation at night time before going to sleep can precisely release the drug after midnight to have its action in the early morning. Few potential candidates for stated need and fit are indomethacin, tramadol, prednisone (for rheumatoid arthritis); salbutamol, terbutaline (for asthma); verapamil and diltiazem (for angina pectoris)[1,6]. In another approach, drugs with shorter half lives may also be rationalized for multi-pulse release formulations facilitating repetitive burst release of low doses. Here, first dose releases instantly to attain therapeutic drug concentration and subsequent doses release with intermediate lag time which is approximately equivalent to the duration of action of previous dose. Hence, each pulse releases optimally to maintain the drug concentration in the therapeutic window before it starts falling in sub-therapeutic level. The drugs like methylphenidate (attention deficit hyperactivity disorder), salbutamol (asthma), terbutaline (asthma), indomethacin (arthritis), tramadol (arthritis), verapamil (angina), diltiazem (angina), etc. can be fabricated for such multi-pulse release formulations. The time to achieve peak concentration with IR formulations of these drugs is around 1–3 h whereas approximate duration of action at their respective recommended minimal doses is around 3–6 h; which in turn becomes the desired intermediate lag time between two

Address for correspondence: Dr Rajashree Mashru, Associate Professor, Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Vadodara 390001, Gujarat, India. Tel: +91 265 2434187; +91 9428977923. E-mail: rajshreemashru@yahoo.com

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RESEARCH ARTICLE

Investigating effects of hydroxypropyl methylcellulose (HPMC) molecular weight grades on lag time of press-coated ethylcellulose tablets

Riddhish Patadia, Chintan Vora, Karan Mittal, and Rajashree Mashru

Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Vadodara, Gujarat, India

Abstract

The research undertaken exemplifies the effects of hydroxypropyl methylcellulose (HPMC) molecular weight (MW) grades of on lag time of press-coated ethylcellulose (EC) tablets. The formulation comprised an immediate release core (containing prednisone as a model drug) surrounded by compression coating with variegated EC-HPMC blends. Five selected HPMC grades (E5, E15, E50, K100LV and K4M) were explored at three different concentrations (10% w/w, 20% w/w and 30% w/w in outer coat) to understand their effects on lag time and drug release. *In vitro* drug release testing demonstrated that, with increase in concentration of E5 and E15, up to 30% w/w, the mean lag time decreased progressively; whereas with remaining grades, the mean lag time initially decreased up to 20% w/w level and thereafter increased for 30% w/w level. Importantly, with increase in HPMC concentration in the outer coat, the variability in lag time (%RSD; $n = 6$) was decreased for each of E5, E15 and E50, whereas increased for K100LV and K4M. In general, the variability in lag time was increased with increase in HPMC MW at studied concentration levels. Markedly, tablets with 30% w/w K4M in outer coat exhibited slight premature release (before the rupture of outer coat) along with high variability in lag time. Overall, the study concluded that low MW HPMCs (E5, E15 and E50) were found rather efficient than higher MW HPMCs for developing robust EC-based press-coated pulsatile release formulations where precise lag time followed by sharp burst release is desired.

Keywords

Chronotherapeutic, compression coating, excipient, pulsatile release, time-controlled formulation

History

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Introduction

Treatment of chronological disorders has, since long time, held the interest of scientists in developing time-controlled pulsatile release (PR) formulations[1–6]. Such disorders are in fact the state of a disturbed circadian rhythm or in other words diurnal imbalance of normal hormonal secretion[7–9]. Apparently, day time control of such disorders can be managed by delivering the medicaments at apt timings but situation is rather difficult in night when patients are asleep. The chronological disorders such as bronchial asthma, rheumatoid arthritis, hypertension, angina pectoris and so on demonstrate peak disturbances in the early morning hours because of disturbed circadian rhythm[2,3,7,10]. Conventional way of treatment for such conditions is to administer either an immediate release (IR) or a sustained release (SR) formulation before going to bed in a dose amount that is sufficient to maintain therapeutic concentration till the next morning. In these cases, as drug is continuously released throughout the night, the dose needs to be kept a little bit higher to extend its effect up to next morning. This higher dose inflicts additional side effects as well as metabolic load on the body even when the effect is not really required. Hence, there is a need to restrict the drug release up to midnight followed by burst release to have the peak effect specifically in the early morning hours only[3,11]. By this way, maximum administered dose can be utilized solely for therapeutic purpose and thereby it will be possible to reduce the requisite dose amount with better management of early morning attacks. Chronotherapeutic drug delivery systems or more precisely time-controlled PR formulations can be useful for achievement of stated goal[2–5]. Administration of such formulations before going to bed can precisely restrict the release according to the desired lag time and subsequent burst release can prevent early morning attacks. The management of such early morning attacks in rheumatoid arthritis (prednisone, indomethacin, tramadol), asthma (salbutamol, terbutaline) or angina pectoris (verapamil, diltiazem) would be better if the respective drugs are delivered in the form of time-controlled PR formulations rather than conventional ones[2,3,11].

Achieving a precise lag time using pH independent polymers is a more convincing approach, since pH induced biological variations will be minimal and the formulation will become truly time-controlled in nature. A swellable core encapsulated by rupturable outer coat, engineered using a combination of water soluble and water insoluble polymers, can be contrived to

Address for correspondence: Dr. Rajashree Mashru, Associate Professor, Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Vadodara 390001, Gujarat, India. Tel: +91 2652434187/9428977923. E-mail: rajshreemashru@yahoo.com

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Research Article

Quality by Design Empowered Development and Optimisation of Time-Controlled Pulsatile Release Platform Formulation Employing Compression Coating Technology

Riddhish Patadia,[1] Chintan Vora,[1] Karan Mittal,[1] and Rajashree C. Mashru[1,2]

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ABSTRACT. The research was envisaged for development of time-controlled pulsatile release (PR) platform formulation to facilitate management of early morning chronological attacks. The development was started using prednisone as a model drug wherein core tablets were prepared using direct compression method and subsequently compression-coated with ethylcellulose (EC)-hydroxypropyl methylcellulose (HPMC) excipient blend. Initially, quality target product profile was established and risk assessment was performed using failure mode and effect analysis. In an endeavour to accomplish the objective, central composite design was employed as a design of experiment (DoE) tool. Optimised compression-coated tablet (CCT) exhibited 4–6 h lag time followed by burst release profile under variegated dissolution conditions *viz.* multi-media, change in apparatus/agitation and biorelevant media. Afterwards, five different drugs, *i.e.* methylprednisolone, diclofenac sodium, diltiazem hydrochloride, nifedipine and lornoxicam, were one-by-one incorporated into the optimised prednisone formula with replacement of former drug. Change in drug precipitated the issues like poor solubility and flow property which were respectively resolved through formulation of solid dispersion and preparation of active pharmaceutical ingredient (API) granules. Albeit, all drug CCTs exhibited desired release profile similar to prednisone CCTs. In nutshell, tour de force of research epitomised the objective of incorporating diverse drug molecules and penultimately obtaining robust release profile at varying dissolution conditions.

KEY WORDS: burst release; chronotherapeutics; failure mode and effect analysis; lag time; risk assessment.

INTRODUCTION

Nowadays, rate of disorders has significantly increased due to drastic change in lifestyle including mental stress and diet which compels consumption of numerous medicines (1–4). Apparently, drugs/medicines are the chemical compounds which possess side effects, normally undergo metabolism and often show drug-drug/drug-food interactions. All of these drawbacks are generally dose dependent which increase with increase in dose. Although administration of these life saving drugs cannot be sojourned, their dosage can be appropriately reduced or adjusted to a suitable effective level so as to minimise associated drawbacks as much as possible. The task can be rationally fulfilled by delivering the drug aptly, *i.e.* only when it is required. The stated approach is quite befitting these days especially in the treatment of early morning chronological attacks (5–7).

Chronological disorders exhibit diurnal variations in their amplitudes owing to circadian rhythm of the body (8,9). Amongst various chronological disorders, bronchial asthma, rheumatoid arthritis, variant/prinzmental's angina, hypertension *etc.* exhibit peak disturbance in the early morning when patients are asleep (10–12). Conventionally, such early morning attacks are treated with bedtime administration of medicines in the form of either immediate release (IR) or extended release (ER) formulations. In such cases, though effect is needed only in the early morning, the drug is continuously released throughout the night; entailing higher amount of dose to extend its effect up to the next morning. Apparently, if this extra dose which releases throughout the night has no therapeutic benefit, it would be considered harmful in terms of side effects as well as increased metabolic load (13,14). Moreover, with compounds having major long-term side effects such as glucocorticoids (15), the situation is even hard hearted. Instead of this conventional approach, if

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[1] Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, 390001, Gujarat, India.
[2] To whom correspondence should be addressed. (e-mail: rajshreemashru@yahoo.com)

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Dissolution Criticality in Developing Solid Oral Formulations: From Inception to Perception

Riddhish Patadia, Chintan Vora, Karan Mittal, & Rajashree Mashru*

Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Vadodara-390001, Gujarat State, India

*Address all correspondence to Rajashree C. Mashru, Associate Professor, Pharmacy Department, Faculty of Technology and Engineering, The Maharaja Sayajirao University of Baroda, Kalabhavan, Vadodara-390001, Gujarat State, India; rajshreemashru@yahoo.com.

ABSTRACT Currently, dissolution testing has become a vital tool for accessing product performance, especially in the hierarchy of solid oral dosage forms. With advances in complicated, expensive, and sophisticated analytical instruments, characterization of formulations has become easier, but simple dissolution assembly is gradually gaining momentum from industrial environs as well as regulatory agencies. As such, simple dissolution testing involves many complexities which must be properly understood to reach correct conclusions. The appropriate selection of multiple parameters (e.g., apparatus, medium, agitation, etc.) involved in dissolution testing and understanding their impact on analysis require thorough subject knowledge. In the words of regulatory provisions, *in vitro* dissolution testing can become a surrogate for expensive and tedious bioequivalence studies in special cases (i.e., when a biowaiver is recommended). As a consequence, reduced human testing as well as lower product development cost ultimately benefit patients and society. Therefore, the dissolution science has recently become one of the keys for success for formulation scientists, especially generic manufacturers. While designing dissolution methodologies, generic manufacturers need to follow the respective regulatory guidelines at the product development stage; concomitant data are required for the approval process. This comprehensive review is an earnest attempt to acquaint readers with the history, contemporary practices, and relevant issues regarding dissolution which may become a guiding tool for overcoming challenges and opening better prospects in product development.

KEY WORDS: discriminating, dissolution, sink condition, biorelevant, bioequivalence, *in vitro in vivo* correlation, biopharmaceutical classification system, biowaiver

ABBREVIATIONS: ANDA, abbreviated new drug application; API, active pharmaceutical ingredient; BCS, Biopharmaceutical Classification System; BE, bioequivalence; BP, British Pharmacopoeia; DoE, design of experiments; DR, delayed release; EMEA, European Medicines Agency; ER, extended release; FaSSGF, fasted-state simulated gastric fluid; FaSSIF, fasted-state simulated intestinal fluid; FDA, Food and Drug Administration; FeSSGF, fed-state simulated gastric fluid; FeSSIF, fed-state simulated intestinal fluid; ICH, International Conference on Harmonisation; IP, Indian Pharmacopoeia; IR, immediate release; IVIVC, *in vitro in vivo* correlation; MR, modified release; NCE, new chemical entity; NF, National Formulary; QC, quality control; RLD, reference listed drug; QbD, quality by design; SCoF, simulated colonic fluid; DBE, Division of Bioequivalence; SGF, simulated gastric fluid; SLS, sodium lauryl sulfate; SUPAC, scale-up and post-approval changes; USP, United States Pharmacopoeia; WHO, World Health Organization

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