International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685; Impact Factor: RJIF 5.28
Received: 19-10-2020; Accepted: 04-11-2020; Published: 23-11-2020
www.pharmacyjournal.net
Volume 5; Issue 4; 2020; Page No. 17-20

An article review on the effect of formulation excipients on drug release characteristics of extended release tablets

Safe Musonda[1], LTM Muungo[2]
[1] Department of Clinical Services, Ministry of Health, University of Zambia, Zambia
[2] Department of Pharmacy, School of Health Sciences, University of Zambia, Zambia

Abstract
Pharmaceutical products, more often than not, contain non medicinal substances known as excipients. They are intended to enhance manufacturing process, make dosage formulation acceptable, bulking up solid formulations that contain potent active ingredients in small amounts and to confer a therapeutic enhancement on the active ingredient in the final dosage form However, their quality and quantity in a formulation may influence release properties of the active drug: As a result, dosage formulation of the same drug by different manufacturers in the same country or different countries might also exhibit a variety of drug release characteristics and this often can affect bio-availability and ultimately clinical effectiveness. Hence, this article review endeavors to appraise the effect of formulation excipients on drug release characteristics of extended release tablets.

Keywords: extended release tablets, excipients, drug release

Introduction

Pharmaceutical products, apart from the active drug ingredient, more often than not contain non-medicinal substances known as excipients (Rutesh, 2008) [30]. They are intended to enhance manufacturing process, make dosage formulation acceptable, bulking up solid formulations that contain potent active ingredients in small amounts and to confer a therapeutic enhancement on the active ingredient in the final dosage form (Allen et Ansel, 2014) [3]. However, their quality and quantity in a formulation may influence release properties of the active drug: As a result, dosage formulation of the same drug by different manufacturers in the same country or different countries might also exhibit a variety of drug release characteristics and this often can affect bio-availability and ultimately clinical effectiveness (Adegbolagam *et al*..., 2017). Drug release is being the process by which a drug product is available for absorption, distribution, metabolism, and excretion, eventually becoming available for pharmacological action (Satinder, 2014). Several studies have affirmed that types of excipients and amount used are likely to affect drug release profiles of controlled release dosage formulations thereby influencing drug bioavailability and utmost therapeutic effect (Lin *et al*...., 2004) [22]. Thus, excipients comparison, equivalence in in-vitro drug release profiles, risk/benefit analysis and in-vivo bio-equivalence assessment can be used to evaluate pharmaceutical equivalence of different brands of extended release tablet formulations (World Health Organisation, 2015).Therefore, appropriate selection of excipients and their relative concentrations in the formulation is important in the development of a successful pharmaceutical formulation because they determine the stability, bioavailability, and processability of the dosage form (Shyne, 2008) [31]. Hence, this article review endeavors to appraise the effect of formulation excipients on drug release characteristics of extended release tablets.

Over more than two decades, it has become evident that marketed products having the same amount of the drug chemical entity may exhibit marked differences between their therapeutic responses (Zuheir and Alaa, 2012). Difference in release characteristics has been attributed source of supply and variation in the types of excipients used, manufacturing process and site of manufacturing (Truus, 2011). In addition, factors specific to controlled release formulations such as Polymer's concentration, drug-to-polymer ratio and to some extent the viscosity grade of the polymer have been found to be responsible for the changes in the release rates of the drugs (Adero, Zarzualo et Lanao, 2011) [23].

Excipients of Extended Release tablets include polymers, binders, glidants, disintegrating agents, filters, lubricants, solvents suspending agents and dyes (Allen, and Ansel, 2014) [3]. It is important to note that development of extended release matrix systems has been a means for optimization of therapeutic effect, by maximizing the bioavailability of conventional drugs (Li XL, 2006).This study specifically investigates the effect of formulation excipients used on drug release characteristics of extended release tablet formulations.

Extended Release drug products are a type of modified release dosage form that allows the slower release of the drug so that plasma concentrations are maintained at a therapeutic level for an extended period of time (Leane *et al*..., 2012). They are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug (Daniel, 2017). The basic rationale of a controlled drug delivery system is to optimize the bio-pharmaceutics, pharmacokinetic and Pharmaco-dynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route (Deepus, 2015) [13]. The goal in designing extended release delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery (Lloyd, 1999).

Extended release is ideal for formulations that have a shorter half-life and high dosing frequency especially in chronic conditions (Rohit and Arjun, 2020).

Polymers as characteristics excipients of extended release tablet formulations

Extended-Release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug (Daniel, 2017). The basic rationale of a controlled drug delivery system is to optimize the bio-pharmaceutics, pharmacokinetic and Pharmaco-dynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug administered by the most suitable route (Deepus, 2015) [13].

Extended-Release drug products dosage form allow at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products (Madan, 2001). Controlled-release action of extended Release formulations is achieved by using polymers that are coated on solid dosage forms or by the incorporation of various types of polymer matrix systems, enzyme-activated systems, or systems that respond to changes in physical conditions within the formulation. Mechanisms include dissolution, diffusion, and osmotic pressure to maintain hydrological or hydrodynamic equilibrium and ion exchange (Caterina, 2019$_b$). Thus, some excipients in Extended Release formulations contribute to the formation of the matrix in the systems that use it and act as polymeric membranes for powders and multi-particulate systems in the forms of oral solid dosage to control drug release characteristic (Catarina, 2019$_a$).

Polymers, in particular, form membranes in a modified tablet matrix that protect the drug from immediate release into the dissolution media. Apparently, Polymers are chains of covalently bound monomers. In relation to oral drug delivery systems they are used as carriers for the drug (Colombo *et al*.... 2000) [7]. As for sustained release formulations the polymers should possesses properties that control and maintain the rigidity of the matrix over a prolonged period (Kim 2000) [19]. There are a large number of polymers that are used in sustained release drug delivery (Maderuelo *et al*.... 2011) [23]: However, there should be enough polymer content to form a uniform barrier: Otherwise. Low level polymer content does permit complete formation of gel layer thereby leading to faster release of active drug (Gamesh *et al*..., 2010).

Polymers can be categorized into two classes, water soluble (hydrophilic) and water insoluble (hydrophobic) polymers. Hydroxypropyl methyl cellulose (hypromellose, HPMC) is a hydrophilic polymer available in several grades that vary in viscosity and extent of substitution so much that they are widely used (Aqualon Product Booklet, 2002). Furthermore, Polymers can either be natural or semi-synthetic and both types can be used as modifiers individually or in combination for Extended release formulations though combination imparts better modifying outcome (Ehab *et al*..., 2015). The natural polymers like agar agar, guar gum, chitosan, xanthan gum and cashew gum have been used in matrix systems of drug delivery. Merits about natural polymers are that they are of low cost; minimum side effects; renewable. Bio-acceptable; environmental friendly processing; locally available and contribute to economic growth (Ganesh *et al*..., 2010). On the other hand, semi–synthetic release modifiers such as hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, hydroxy propyl cellulose and ethylcellulose have been potentially utilized as tablets matrix system (Colombo, 1993; Siepmann *et al*...., 1999; Colombo, *et al*...., 2000; Kiil and Dam, 2003) [9, 32, 7, 18].

Matrix tablets can be formulated by using hydrophilic polymers. That is, hydrophilic matrix tablets containing hydrophilic polymers absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The outermost layer of the matrix eventually becomes diluted to the point where individual chains detach from the matrix and diffuse into the bulk solution (Dipti *et al*... 2015). Hydrophilic matrices are composed of hydrophilic polymers, an active ingredient and other excipients homogeneously distributed in a three dimensional network. Several factors affect the drug release from a hydrophilic matrix (Conte *et al*...., 1988; Colombo *et al*...., 1999) [8,]. These factors are the drug solubility, polymer swelling, polymer erosion, drug dissolution/diffusion characteristics, distribution of drug within the polymer matrix and proportion and geometry of the system (Wu, Zhou, 1998; Zhou, Wu, 1997; Adrover *et al*...., 1996) [35,]. The absorption of solvent, as well as the drug release, also depends on the viscoelastic properties of the polymer (Crank, 1975) [10]. Thus, drug release from hydrophilic matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms (Maderuelo, Zarzuolo & Lanao, 2011 [23].

As alluded to in the foregoing, polymers vary in type, characteristics and grades. Moreover, manufacturer recipe can differ in terms polymer mix and manufacturing procedure. Therefore, there is a high likelihood that Dosage formulation of the same drug by different manufacturers in the same country or different countries would vary in drug release profiles.

Effects of other excipients on drug release profiles of extended release tablets

Excipients in controlled release table formulations other than polymers release modifiers impart manufacturability, appearance and performance (Pharmapproach, 2020) [29]. They are characterized with their fields of functions as base material, binder or granulating agents, glidants, lubricant and disintegrant (Mario, 2015$_a$). Excipients used in table formulation include bulk agents/diluents/fillers, binders and disintegrants (Mario, 2015$_b$). They are classified in two main classes: That is, those that impart satisfactory processing and compression properties to the formulation, and those that add desirable physic0-chemical characteristics to the compressed tablet (Caterina, 2019) [5]. Thus, excipients in tablet dosage forms enable repeatable accurate dosing, quality, efficacy, safety, stability, over and above, high patient acceptance and compliance (Elder, Kuentz, Holm, 2016) [15]. Furthermore, some excipients have been developed for specific purposes such as effective delivery of active ingredients to the systemic circulation after administration (Abrantes, Duarte, Reis, 2016) [1]. Numerous studies have demonstrated that different categories of excipients have a valuable effect on the solubility and dissolution of active pharmaceutical ingredients (Janner *et al*..., 2020). Accordingly, the quality of final dosage form in terms of stability, dissolution and bio-

availability are mostly dependent on the excipients preferred, their concentration and interaction with both the active compound and each other (Raymond *et al...*, 2009). As a result, with the right excipients, formulators can control when, where, and how an active drug is released (Cynthia, 2018_a) Hence, the theme of this study to assess the effect of quality of excipients on drug release profiles of different brands of tablet formulation with a specific reference to extended release tablet formulations.

Diluents are critical excipients in tablet formulation that are intended to make up the required bulk of the tablet when content of the active drug is insufficient to produce the bulk that is easier to administer (Okafer, 2000). Moreover, they increase weight and improve content of uniformity (Pandey, 2009). Nonetheless, diluents are likely to affect active drug release dynamics. Indeed, Studies have shown that when compressing drugs with low aqueous solubility, the solubility of diluents selected is very crucial as it influences the disintegration, dissolution and bioavailability of such drugs (Umeh, Azegba and Ofoefale, 2013). Meanwhile, diluents can considerably affect the chemical and physical properties of the final tablet that has a bearing on biopharmaceutical profile (Rutesh and Dave, 2008) [30].

Binders are described as additives to tablet solid formulation that are used to hold the active drug and inactive ingredients together in a cohesive tablet mass (Ymecko et Rhodes, 2005). The major categories of tablet binders are sugars, natural and synthetic/semi-synthetic polymers that can used in tablet formulation (Sanethra, Samaranthunga and Folahan, 2016_a). They facilitate enlargement of granules to the intended size so as to enhance free flow of powders during the process of tabletting (Barbosa *et al...*, 2008). Binders also allow inter-granular binding and guarantees that the tablet remains intact after compression (Larry et Augsburger, 2008) [20]. The mechanism of binders is that when they are added to powder diluents mixtures in form of slurry, suspension or solution, liquid links are developed between particles such that bonds increase with the amount of liquid present in the binder (Hemanth, 2014) [16].

It is worth noting that, the nature and concentration of a binder influence the characteristics of compressed tablets and there is a broad spectrum of substances that are used as binders in tablet formulations (Miller et Parikh, 1997) [25]. Besides, studies have demonstrated that physico-chemical properties, type, quality and concentration of the binder affect disintegration and dissolution characteristics of a tablet formulation. Ultimately, this affects the quality of a tablet (Sanethra, Samaranthunga and Folahan, 2016_b).

Another class of excipients that have effect of drug release profile is disintegrants or rather disintegrating agents. To be precise, these are raw materials added to tablet formulations in order to overcome the cohesive strength imparted during compression to facilitate the breakdown of the tablet into granules so that the active drug is available once they are in contact with GIT fluids (Carter, 2006) [6]. This process is achieved by an increase in the porosity and wetting of the compressed tablet matrix: That is, Mechanisms through which disintegrants break dosage forms up into smaller parts include swelling, heat generation due to increased interaction between particles, exothermic wicking action, particle repulsion and recovery of particle deformation (Onuki *et al...*, 2018) [27]. Thus, disintegration is achieved by the penetration of the physiological fluid into the powder compact and the subsequent disruption of the particle-particle bonds which maintain the structural integrity of the dosage form. Therefore, liquid penetration (or wicking) is one of the key steps involved in the disintegration process. The rate of penetration of liquid into a porous matrix is driven by the interplay between the capillary forces that promote fluid movement towards the interior and the viscous forces that oppose the liquid movement. Liquid retention and flow in unsaturated porous media, where the pores are filled with both liquid and air, are thus driven by the balance between cohesion among the liquid molecules and adhesion between the liquid molecules and the particle surfaces (Symkiewicz, 2015).

Factors that influence action of disintegrants include concentration in the recipe, type of disintegrant used, interaction with other excipients in the formulation and chemical nature of the active drug ingredient (Cynthia, 2018_b). Therefore, although different brands of a pharmaceutical product may have same dosage formulation and same strength, their release profile could differ because of the characteristics of a disintegrating agent employed.

Conclusion

This article has reviewed that each excipient in a formulation has influence on the drug release characteristics. More so, the quality and quantity of excipient is likely to have an effect on the rate of the release of the active drug from the tablet matrix of an extended release formulation. Incidentally, this may occasion variations in active drug release profile of different products of the same active ingredient, same dosage formulation and identical in strength or concentration.

References

1. Abrantes CG, Duarte D, Reis CP. an Overview of Pharmaceutical Excipients: Safe or Not Safe: J Pharm Sci, 2016.
2. Aderuelo C, Zarzuelo A, Lanai JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Release, 2011.
3. Allen LV, Ansel HC. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems: Philadelphia: Lippincott Williams and Wilkins, 2014.
4. Barbosa-Canovas GV, Ortega-Rivas E, Juliano P, Yan H. Food Powders: Physical Properties, Processing, and Functionality; Kluwer Academic/Plenum Publishers: New York, USA, 2005.
5. Catarina Lucchini. excipients for controlled release: Pharma world, 2019.
6. Carter John C. The role of disintegrants in solid oral dosage manufacturing: Carter Pharmaceutical Consulting Inc, 2006.
7. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: gel-layer behavior, mechanisms and optimal performance: Pharm. Sci. Technol, 2000.
8. Conte U, Colombo P, Gazzaniga A, Sangalli ME, La Manna A. Swelling-activated drug delivery systems: J Biomaterials, 1988, 489-493.
9. Colombo P, *et al....* swelling controlled release in hydrogel matrices for oral route- Advanced drug delivery review. 1993; 11:37-57.
10. Crank J. The mathematics of diffusion, second Ed: Clarendon Press, Oxford, 1975.
11. Cynthia A. Challener, Selecting Excipients for Controlled Release: Pharmaceutical Technology, Pharm.

Tech.com. 2018; 42(7):24-26.
12. Daniel Mark et Axel Zeitle, A review of disintegration mechanisms and measurement techniques: PMCM, 2018.
13. Deepu S. Formulation and evaluation of controlled release oral hypoglycemic tablets: Vinayaka, Mission University, 2015.
14. Dixit Navin, *et al.*... Sustain release drug delivery system. Indian journal of research in pharmacy and biotechnology. 2013; 1(3):305-310.
15. Elder DP, Kuentz M, Holm R. Pharmaceutical excipients: Quality, regulatory and biopharmaceutical considerations: Eur J Pharm Sci, 2016.
16. Hemanth G Vineath. effect of binders on tablets: Stream, 2014.
17. Jannes van der Merwe, Jan Steenekamp, Dewald Steyn, Josias Hamman. The Role of Functional Excipients in Solid Oral Dosage Forms to Overcome Poor Drug Dissolution and Bioavailability: pharmaceutics, 2020.
18. Kiil S, Dam JK. Controlled drug delivery from swellable hydroxypropyl methyl cellulose matrices: Model-based analysis of observed radial front movements: J Control, 2003.
19. Kim C. Controlled release dosage form design: Florida, USA: CRC Press, 2000.
20. Larry L, Augsburger SWH. Pharmaceutical Dosage Forms: Tablets, 3rd ed.; CRC Press: New York, NY, USA, 2008.
21. Leane M, Pitt K, Reynolds G, Manufacturing T, Leane M, Pitt K, *et al.*... A proposal for a drug product manufacturing classification system (MCS) for oral solid dosage forms: Pharm Dev Technol. 2015; 1(20):12-21.
22. Lin SY, Li MJ, Lin KH. Hydrophilic excipients modulate the time lag of time controlled disintegrating press coated tablets: AAPS Pharm Sci Tech, 2004.
23. Maderuelo A, Zarzuelo J, Lanao. Critical factors in the release of drugs from sustained, 2011.
24. Mario Helmis, Badir Mohamad, Mont Kumpugdee-Vollrath. Influence of several excipients on drug realize of tablets containing resverato: Mathews open access journal, 2015.
25. Miller R, Parikh D. Handbook of Pharmaceutical Granulation Technology; CRC Press: Boca Raton, FL, USA, 1997.
26. Narasimhan B, Peppas N. Molecular analysis of drug delivery system controlled by dissolution of the polymer carrier: J Pharm Sci. 1997; 86:297-304.
27. Onuki Y, Kosugi A, Hamaguchi M, Marumo Y, Kumada S, Hirai D, *et al.*... A comparative study of disintegration actions of various disintegrants using Kohonen's self-organizing maps: Sci. Technol, 2018.
28. Pandey VP, Venka k, Teswara RA, Amaranath R. studies on diluents for formulation of tablets: Int j Chem SCI, 2009, 7(4).
29. Pharmapproach. excipients used in the manufacture of tablets: Pharmapproach.com, MDPI, 2020.
30. Rutesh Dave. overview of pharmaceutical excipients in tablets and capsules: Ukafor N M, 2008.
31. Shayne CG. Pharmaceutical Manufacturing Handbook Production and Processes: New Jersey: John Wiley & Sons, Inc, 2008
32. Siepmann J, Kranz H, Bodmeier R, Peppas NA. HPMC-matrices for controlled drug delivery: A new model combining diffusion, swelling and dissolution mechanisms and predicting the release kinetics: Pharm. Res, 1999
33. Szymkiewicz A. modeling water flow in unsaturated porous media- accounting for non-linear permeability and material heterogeneous: Berlin Heidelberg, spring, 2013.
34. World Health Organisation. WHO expert committee on specifications of pharmaceutical preparations: WHO, Geneva Switzerland, 2018.
35. Wu XY, Zhou Y. Finite element analysis of diffusion drug release from complex, 1998.
36. Ymecko C, Rhodes C. Binder functionality in tablet systems: Drug Dev. Ind. Pharm, 1995.
37. Zuheir Osman, Alaa Elmardi Osman, Aminah M, Abedelghayoum. comparative evaluation of physicochemical properties of some commercially available brands of Metformin HCL tablets marketed in Sudan: Indo America Journal for pharmaceutics, 2004.
38. Pandey VP, K Venkateswara Reddy, Amarnatha R. studies on diluents for formulation of tablets influence of several excipients on drug release of tablets containing resveratrol.
39. Dash A, Singh S, Tolman J. Pharmaceutics: Basic Principles and Application to Pharmacy Practice. USA: Elsevier Inc, 2014.
40. Jones D. Fast-track Pharmaceutics – Dosage Form and Design: London: Pharmaceutical Press, 2008.
41. Okafor S, Ofoefuel SI, Udeala OK. A Comparative Study of Modified Starches of a Water Soluble Drug Chloroquine Phosphate, PMID: 11213430, PUBMED Indexed for MEDLINE, 2008.
42. Szymkiewicz A. Modelling water flow in unsaturated porous media: accounting for nonlinear permeability and material heterogeneity, Berlin Heidelberg: Springer, 2013, 9.
43. Ayush Garg, Amul Mishra. An overview on bilayer tablet dosage forms. International Journal of Research in Pharmacy and Pharmaceutical Sciences, 2020:5(1):15-22.