

DOI: 10.21767/2471-299X.1000043

Pharmaceutical Developability of Clinically Relevant Flavonoids like Curcumin: Why are We Failing?

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Received date: January 30, 2017; Accepted date: February 13, 2017; Published date: February 20, 2017

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Citation: Pratap Singh D, Jayanthi C, Joshi Hanumanthachar K, Pharmaceutical Developability of Clinically Relevant Flavonoids like Curcumin: Why are We Failing? Med Clin Rev. 2017, 3:1.

Abstract

Flavonoids are promising therapeutic class of polyphenolic biomolecules with the potential to alleviate many severe disease states with multi-factorial pathogenesis because of their inherent ability to regulate key biological cascades at the molecular, cellular and organism levels. However, these important polyphenolic compounds frequently pose drug delivery challenges to scientists and produce inefficient pharmacokinetic-pharmacodynamic activities. Importantly, despite their therapeutic potential and the focus of the scientists being on the formulation development front in the recent years, developing an ideal drug delivery system for some of the most important polyphenolic biomolecules such as curcumin is still a challenge. Hence, the basic intent of writing this article is to bring back the focus of the formulation scientists on one of the key physicochemical properties of these important biomolecules i.e., the importance of pH-stability profile of flavonoids, which could play vital role in the formulation developability aspects of important biomolecules such as curcumin by the selection of an ideal dosage form.

Keywords: Pharmaceutical developability; Curcumin; Solubility; Stability; Flavonoids

Introduction

Flavonoids are promising therapeutic class of polyphenolic biomolecules with the potential to alleviate many severe disease states because of their inherent ability to regulate key biological cascades [1-7]. These important polyphenolic biomolecules have received considerable attention in the recent past as summarized [8-10]. Curcumin which is chemically 1,7-bis (4-hydroxy-3-methoxyphenol)-1,6 heptadiene-3,5-dione or diferuloylmethane, is one such polyphenol belonging to a class of compounds known as curcuminoids, isolated from the Indian spice *Curcuma Longa*

which has been used as an Ayurvedic medicine from thousands of years [11,12]. Just like another well studied biomolecule, quercetin [5-7,13,14], curcumin has also received considerable attention over the past decades, which is mainly due to its diverse biological activities, including but not limited to antioxidant, anti-inflammatory, anti-arthritis, anti-ulcer, anti-diabetic, anti-bacterial activities and its potential therapeutic applications in a large number of diseases including but not limited to cancer and neurodegenerative diseases (Figure 1) [4,11,12,15-19]. Hence, curcumin is used as a supplement/neutraceutical in several countries, including but not limited to India, Japan, America, Thailand, China, Korea, Turkey, South Africa, Nepal, Bangladesh, Sri Lanka and Pakistan owing to its perceived potential health benefits [20].

Curcumin Research: What is the Current Scenario?

In human clinical trials, curcumin has been found to be safe and efficacious, and the U.S. Food and Drug Administration has thus approved curcumin as a "Generally Regarded as Safe (GRAS)" compound [21,22]. Nonetheless, although inexpensive, apparently well tolerated, and potentially active, curcumin has yet not been approved for treatment of any human disease/ailment [20]. Despite thousands of research papers, wide range of pharmacological activities of curcumin reported in the past decades, more than 120 reported clinical trials, still a paradox and uncertainty remains regarding the pharmacology of curcumin owing to its physicochemical properties leading to the poor systemic bioavailability [23,24]. Such is the present scenario, that, on one hand some groups in the scientific community believes that curcumin is an ideal drug candidate owing to its reported and perceived therapeutic benefits, and on the other hand some other groups have clearly said that working on curcumin is simply "waste of time" [10,23,24]. However, in between these two schools of thoughts, there is an area of research which needs to be focused and indeed, now, the time is apt to apply the inter-disciplinary approach for the pharmaceutical developability of curcumin.

Curcumin has been reported to mitigate the mitochondrial dysfunction and Adenosine Tri Phosphate (ATP) loss [25], generation of Reactive Oxygen Species (ROS) [26], rise in the levels of nuclear factor kappa B (NF-KB) and pro-inflammatory cytokines like tumor necrosis factor [27-29] and prevents Tight Junction (TJ) dysfunction and thereby Intestinal Permeability (IP) alteration [30].

thoughtful application of the pH-stability profile data in the development of the ideal dosage forms for flavonoids so that this promising class of natural molecules could be brought in the forefront of our armamentarium against variety of diseases.

Developing curcumin loaded gastroretentive drug delivery system (GRDDS): The way forward

In light of the physicochemical properties of curcumin, delivering curcumin as a Gastroretentive Drug Delivery System (GRDDS) would be an ideal approach to perk up the effectiveness of curcumin by prolonging its gastric residence so that the drug is released in the vicinity of its absorption window for an extended period of time and remains stable too [43-47]. Among the numerous approaches used to improve the gastric residence time of Drug Delivery System (DDS), the vital ones include, single and multiple-unit floating systems, bioadhesive systems, swelling unfoldable and expanding systems, raft forming systems and high-density systems [43-46]. However, while selecting the ideal approach of gastric retention for curcumin, the solubility cum stability profile of curcumin should be kept in mind so as to have a stable delivery system with ideal dissolution characteristics.

Discussion and Conclusion

Advancements in modern science have provided a scientific basis for the practice of using turmeric and/or curcumin therapy against numerous human diseases/ailments in innumerable cultures and societies in many countries. This important polyphenolic biomolecule (curcumin) has been shown to target multiple signaling molecules and has shown activities at the molecular, cellular and organism levels that provide a basis for its use against variety of human diseases with multi-factorial pathogenesis. The scientific fraternity is today looking for ways to address the issues related to the pharmaceutical developability of curcumin. In this purview, one of the major concerns associated with the pharmaceutical developability of curcumin is its low oral bioavailability that can be attributed to its low solubility, poor absorption, high instability in alkaline media and rapid elimination from the body. Numerous approaches including the nanotechnology based delivery systems have been reported in the literature so as to enhance the bioavailability of curcumin. However, looking at the physico-chemical properties of curcumin and its therapeutic potential, developing curcumin based GRDDS could be highly beneficial. Therefore, further research is required to determine the optimal dosage, bioavailability, and bio-efficacy of curcumin-based GRDDS in the near future. We believe that this approach could be highly beneficial in answering at least some questions related to the paradox and uncertainty around curcumin. Translation of this knowledge is eagerly awaited.

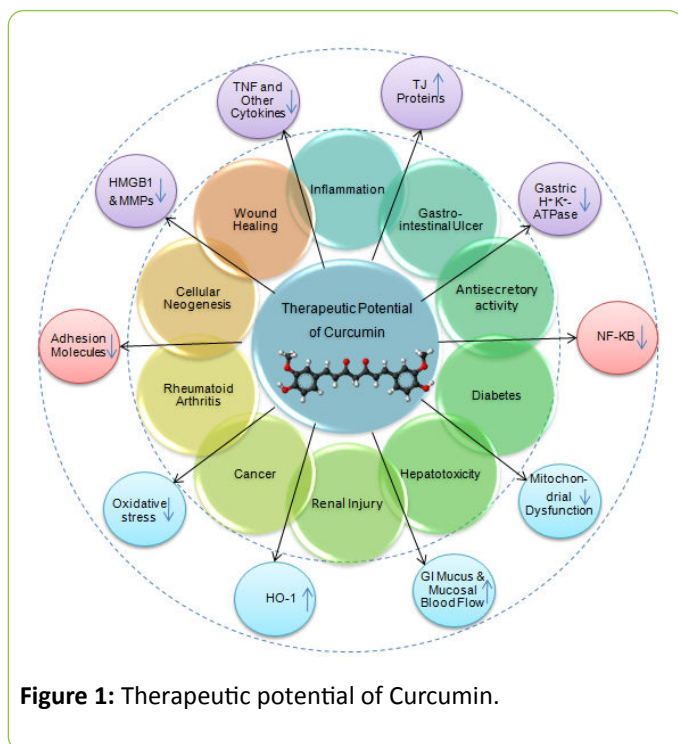


Figure 1: Therapeutic potential of Curcumin.

It has been demonstrated to downregulate high mobility group box 1 (HMGB-1) [31] and Matrix Metalloproteinases (MMPs) levels [26], enhance haeme oxygenase-1 (HO-1) levels [32], decrease adhesion molecules [28] and has been shown to inhibit gastric $H^+ K^+$ -ATPase activity [33], which have been identified as some of the important players in the etio-pathogenesis of variety of diseases against whom the potential of curcumin has been reported in the scientific literature.

Designing an Ideal Drug Delivery System for Curcumin: What's New?

Curcumin faces many challenges in relation to its successful pharmaceutical developability, which are mainly related to its low solubility and stability in physiologically relevant solutions. Indeed, many researchers have highlighted previously that, curcumin is hydrophobic in nature and is highly unstable undergoing rapid hydrolytic degradation in neutral or alkaline conditions, but is stable below pH 6.0 [34-36]. In addition, there is yet another challenge; curcumin is insoluble in water under acidic or neutral conditions but dissolves in alkaline environment; the solutions in which it is unstable. Many dosage forms incorporating curcumin including the nanotechnology-based novel strategies have been reported in the literature [4,15,37-42]. However, while designing the dosage forms for curcumin, the data related to the stability profile of the curcumin has been overlooked. Here, in the present paper, authors emphasize on the opportunities for the

Acknowledgement

Authors are thankful to management of Sarada Vilas College of Pharmacy, Mysore, Karnataka, for providing all the facilities for the successful completion of the work.

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