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Design and mechanistic evaluation of novel pore-regulated polymer matrices for transmucosal drug delivery

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CHAPTER EIGHT

CONCLUSIONS AND RECOMMENDATIONS

8.1. CONCLUSIONS

Porous structured devices are becoming significantly relevant in the area of pharmaceutical sciences because of their unique and attractive characteristics such as stable porous configuration, high surface area, flexible pore dimensions arranged in various distributions and patterns as well as their highly-defined surface properties which can allow for easy manipulation of their drug loading efficiency, rate of drug delivery, enhanced bioadhesion to mucosal sites and permeation enhancements for the systemic delivery of drug molecules.

The transbuccal route of drug delivery is a preferred method of transmucosal drug administration as it is very accessible for easy self administration, has short recovery times after stress or damage, has an expanse of robust, smooth muscles, is rich in blood supply, has direct access to the systemic circulation through the internal jugular vein which allows drugs to bypass the pre-systemic metabolic processes in the gastrointestinal tract and/or hepatic first pass effect thus leading to an increased bioavailability, has relatively rapid onset of action and displays little or no mucosal irritation. Other merits such as painless administration, versatility and simplicity, easy dosage form withdrawal whenever needed and the ability to include permeation enhancers, enzyme inhibitors, pH modifiers or bioadhesive compounds and other relevant pharmaceutical additives in the formulation for local or systemic actions.

The transbuccal route of delivery employing porous drug delivery devices appears to be a promising option for effective pharmacotherapy because, as far as we know, transbuccal drug delivery focused extensively on the use of formulations that are not porosity-enabled such as tablets, gels and pastes. Therefore, it is needful to construct and explore the novel bioadhesive, biodegradable, biocompatible, permeation enhancing pore-regulated polymer matrices described in this work for prolonged drug release for transbuccal applications.

The systematic design of experiments employing the highly efficient statistically and mathematically robust Box-Behnken design approach is a dependable scientific tool in developing, characterizing, exploring and optimizing distinctive porosity-enabled drug delivery systems. Suitable design templates can be selected to achieve the desired experimental outputs. Consequently, the influence of formulation variables on the overall physicochemical

and physicomechanical characteristic of the pore-regulated polymer matrix during preparation as well as its statistical optimization process were investigated.

An interphase, co-particulate, co-solvent, homogenization technique coupled with pre-freezing and lyophilization were employed. The choice of method of preparation was based on its simplicity and optimum efficiency in generating robust and stable porous formulations which would enable an undemanding industrial process operation and minimized production cost enhancing patient affordability.

The versatility of the optimized pore-regulated polymer matrix was assessed utilizing phenytoin sodium and carbamazepine as model drugs. The pore-regulated polymer matrix formulation was stable as the separate inclusion of the model drugs with differing physical properties did not significantly alter the measured physicochemical and physicomechanical parameters of the formulation. Besides, the direct or indirect impact of porosimetric parameters, namely average pore diameter and cumulative surface area of pores, on the magnitude of selected measured physicochemical and physicomechanical were also noted.

The *in vivo* quantitative and qualitative evaluation of the newly constructed optimized pore-regulated polymer matrix was performed using the pig as an animal model. These formulations demonstrated the potential to effectively aid and regulate the systemic release of both phenytoin sodium and carbamazepine through the transbuccal route of drug administration. Comparisons were made between the pore-regulated matrix formulation and the commercially available oral formulations using drug plasma level versus time profiles. It was observed that the porous matrix was more efficient in terms of plasma levels, dosage and duration of absorption. The performed non-compartmental PK-PD modeling fitted the investigated *in vivo* data accurately and generated relevant pharmacokinetic and pharmacodynamic parameters which showed the differences in the performances of the assessed formulations. The point-to-point level A IVIVC correlation model developed for the PS and CBZ loaded P-RPM formulation was linear (R^2 > 0.9) indicative of the possibility of applying its *in vitro* dissolution profiles as a surrogate for bioequivalence studies especially when changes are made during production. Histological and cytological studies showed that the placebo or drug loaded P-RPM formulation had no significant toxic or irritating influence on the buccal mucosal specimen as well as the cell cultures employed.

Based on the known morphological flexibility and complexity of porous devices, this study attempted to elucidate the underlying mechanisms potentially guiding the construction and performance of the novel pore-regulated polymer matrix formulation using both experimental and computationally modelled processes. Experimental assays showed that the fabrication process of the pore-regulated matrix formulation was based on structurally, non destructive, reversible physical and mechanical transitions which implies that the overall behaviour of the formulation is dependent on the contributive effects of the component compounds. In addition, it was noted that the mechanism of action of the porous formulation was mainly attributable to the disruption of the ordered porous structure of the pore-regulated matrix. The outcome of the experimental analyses was further substantiated by the application of computational molecular modeling.

A preliminary investigation of the effects of scale-up and common environmental storage conditions on the physicochemical and physicomechanical properties of the pore-regulated polymer matrices showed that scale-up may not significantly alter the established characteristics of the formulation and that the formulations are most stable under controlled humidity, exposure to light and room temperature storage conditions.

8.2. RECOMMENDATIONS

With regards to prospective researches, it is recommended that the pore-regulated polymer matrix developed in this study be assessed extensively for their *in vivo* performance in terms of bioavailability and biocompatibility especially due to repetitive use employing healthy human volunteers since the initial use of animal models and mammalian cell lines for the toxicity studies have proven to be successful. This will further establish the efficiency of these drug delivery systems which are anticipated to function for management of chronic disease conditions such as epilepsy, diabetes, hypertension, tumours and malignancies and joint disabilities (e.g. arthritis) in which cases patient compliance can be a major challenge as well as the delivery of drug substances which are susceptible to first pass metabolism as well as gastrointestinal degradation. Although the *in vivo* animal studies may supply valid information regarding the performance of the formulation under physiological conditions, they may also completely simulate the conditions in the human biological systems.

It is also proposed that extensive research be conducted to ascertain the important biochemical processes and pathways involved during the metabolism of the pore-regulated polymer matrix formulation despite that its components are biocompatible in nature.

It is essential that the versatility of the pore-regulated polymer matrix formulation be further explored employing a wider range of drug substances and bioactives.

A retest of product stability using validated analytical procedures may be necessary especially to assess microbiological stability and determine the shelf life with regards to commercialization of the formulation.

For larger scale industrial applications, it may be necessary to re-evaluate the physicochemical and physicomechanical properties of the pore-regulated polymer matrix for consistency.

Additionally, more research can be executed in the area of understanding the underlying mechanisms guiding the fabrication and performance of the pore-regulated polymer matrices as this may serve as useful tool in the area of inventing such attractive porous systems for other drug delivery applications.

Overall, the outputs of this research in relation to the performance of the P-RPM drug delivery system may be of significant value to pharmaceutical and polymer scientists working in the field of drug delivery and other related areas.