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Role of butter oil in brain targeted delivery of Quetiapine fumarate microemulsion via intranasal route

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ABSTRACT

Purpose of the present investigation was to explore the potential of butter oil (BO) as a novel permeation enhancer to enhance the drug concentration in the brain when given intranasally. Quetiapine fumarate (QF) was selected as a model drug since it undergoes extensive first-pass metabolism leading to poor oral bioavailability of 9%. QF:BO binary mixture was prepared by simple physical mixing in the ratio of 1:9 to 9:1. Diffusion study was performed to obtain optimized QF:BO ratio. QF loaded microemulsion (ME) system (QF ME) was developed by water titration method. The optimized ratio of QF:BO showing higher permeation for QF was added into ME to obtain QF:BO ME. Globule size of QF ME and QF:BO ME was found be 61.59 ± 0.54 and 133.30 ± 1.74 nm, respectively. Nasal diffusion data revealed that QF:BO ME showed higher permeation (85.45 ± 2.14%) for QF in comparison to QF ME (52.07 ± 2.07%) and QF solution (40.00 ± 2.01%). Nearly 4.6 folds higher brain bioavailability of QF:BO ME (384.11 ± 49.10%) compared to QF Solution (83.15 ± 9.82%) suggested higher transport of QF from QF:BO ME to rat brain. Overall, it was concluded that BO enhances the brain bioavailability of poorly permeable drugs across the olfactory neuroepithelium, thereby proving its potential in the area of brain drug delivery system.

1. Introduction

In recent year, intranasal drug delivery has emerged as a potential non-invasive method for the delivery of drug, protein, and peptides to the brain by circumventing blood-brain barrier and avoiding the first-pass metabolism thereby providing rapid absorption and enhancing drug influx at the blood-brain barrier. The presence of rich vasculature structure and direct connection between olfactory and trigeminal region helps in delivering therapeutics into the brain by minimizing systemic exposure. The benefits of the intranasal route to the CNS include avoidance of trauma to the brain or implantation of foreign bodies and reduced side effects associated with systemic administration. These include hepatic first pass effect, systemic dilution effect, drug delivery to off target sites, and the need for higher doses [1].

The transport of drug from nose to brain occurs via the olfactory epithelium, which serves as the gateway for substances entering the CNS and the peripheral circulation. The olfactory pathway provides both an intraneuronal pathway and extraneuronal pathway into the brain [2,3]. The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain region. The extraneuronal pathway, however relies on the bulk flow transport through perineural channels, which deliver drugs directly to brain parenchymal tissues and/or Cerebrospinal fluid. Thus with the extraneuronal pathway, the therapeutics reaches CNS within minutes. Absorption of the drug through nasal mucosa involves its passage through the mucus. Small uncharged particles easily cross the mucosa, however, large or charged particle finds it difficult to cross the mucosa. After passage through mucus, the drug may be absorbed from mucosa either by simple diffusion across the membrane, paracellular transport via movement between the cells or transcytosis by vesicle carriers [4].

Although the intranasal route is efficient for topical, systemic and CNS delivery of a wide range of drugs, it cannot be applied to many others due to their low nasal bioavailability. Briefly, the bioavailability of nasally administered drugs is particularly

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restricted by low drug solubility, rapid enzymatic degradation in the nasal cavity, poor membrane penetration and rapid mucociliary clearance [5].

Several approaches have been suggested to overcome these limitations, including the use of prodrugs, enzymatic inhibitors, absorption enhancers, and development of mucoadhesive delivery systems. To overcome the problem of poor membrane permeability, the most frequent used approach is the use of permeation enhancers. Different permeation enhancer loaded products are reaching to the clinical trials like CriticalSorb® (based on Solutol HS15) (Critical Pharmaceuticals Ltd), ChiSys® based on chitosan (Archimedes Pharma Ltd) and Intravail® based on alkylsaccharides (Aegis Therapeutics Inc.). Up to now, none of these permation enhancers have been used in a marketed nasal product, although at least a morphine-chitosan product (i.e. Rylomine®, Javelin Pharmaceuticals, a subsidiary of Hospira Inc.) has reached Phase 3 clinical trials [6]. However, the precise mechanism of their action is not known but they may work by a different mechanism like increasing membrane fluidity, expanding the dimension of the paracellular pathway to solute transport, creating transient pores by reverse micelle formation in the cell membrane or combination of more than one mechanism [7]. The approval of a permeation enhancer is not only given based on its ability to enhance absorption but also on its overall safety profile with respect to both local and systemic effects [8].

In the current proposal, we have used butter oil (BO) of cow origin as a novel lipidic permeation enhancer. BO is a concentrate of butterfat with more than 99% of milk fat and less than 0.2% moisture. BO is prepared by the indigenous route involving fermentation of milk by cultures of Lactobacillus into curd and subsequent churning of curd into butter followed by clarification [9,10]. Some of the important saturated and unsaturated fatty acids reported to be present in BO includes Butyric acid, Caproic acid, Caprylic acid, Capric acid, Lauric acid, Myristic acid, Palmitic acid, Stearic acid, Hexadecenoic acid, Oleic acid, Linoleic acid, and Linolenic acid. It is reported that lipids of ruminant milks are unique with enormous range and diversity in the structure of fatty acids and other minor components which includes long chain bases and alkyl and alk-1-enyl ether residues with some of them having their origin in rumen bacteria. It is also mentioned that the process of hydrogenation and isomerization of feed lipids by rumen microorganism together with possible modification in cow itself produces an extremely complex mixture of monoenoic and dienoic acids. In ayurvedic system of medicines, BO is an integral part of ghritapaka, in which paste of medicinal herbs exhibiting therapeutic activity are homogenized with BO and subsequently heated till the active ingredient is extracted in BO and it acquires characteristic odour/colour of the herb. Though therapeutic benefits of BO are known in Ayurveda since ancient times, its use in the modern system of medicines is not yet fully explored. Besides its numerous therapeutic activities, BO is used as preferred carrier or adjuvant in many ayurvedic formulations owing to its favorable properties like pharmacological inertness, nontoxic, nonirritant and compatible nature [11–13].

Individually few of these fatty acids are known permeation enhancers [14–16]. The current proposal has its roots in the fact that when individually these fatty acids can act as permeation enhancers, BO which combines all these fatty acids could be also retaining few of these properties and may exhibit higher permeation than individual fatty acids alone. Some of the previous work on BO obtained from Cow reported that it possesses ability to alter the bioavailability of some drugs by sustaining their release from dosage forms meant for topical as well as systemic administration [17,18]. The utilization of these properties of BO in making pharmaceutical dosage forms seems attractive, because of the total lack of toxicity and already existing prevalence of its use as a food ingredient in terms of safety.

With this background, in the current proposal, we intend to make use of BO of cow origin as a novel permeation enhancer to study its effect on enhancing permeation across nasal mucosa and help in achieving brain targeting when administered via intranasal route. Quetiapine fumarate (QF), which is a novel antipsychotic agent with broad efficacy, and elicits a response in both positive and negative symptoms of schizophrenia and bipolar disorder, was selected as a model drug for this study. QF is a BCS Class II drug which is poorly water soluble and may show dissolution-limited absorption. It exhibits pH dependent solubility; therefore, low absorption is expected at higher pH environment. It has a plasma half-life of 6 h and oral bioavailability of only 9%. Besides this, the clinical usefulness of QF is limited by its high first-pass metabolism effect and poor entry through blood–brain barrier, the prime reason for selecting it as a model drug [19,20].

To evaluate the role of BO in facilitating nose to brain drug delivery, QF based microemulsion with and without BO is developed and characterized for physicochemical, nasal permeation study, morphological parameter, histopathological study, and pharmacokinetic parameters.

2. Material and method

2.1. Material

Quetiapine fumarate and risperidone were received as a gift sample from Torrent Pharmaceuticals Ltd. (Ahmedabad, India). Cremophor EL, Cremophor RH 40 and Polyethylene glycol 400 were received as gift samples from Signet chemicals corporation Pvt. Ltd. (Mumbai, India). Capmul MCM EP, Acconon MC8-2 and Captex 200-P were provided as gift samples from Abitec Corporation Ltd. (Mumbai, India). Capryol 90, Labrafac lipophile WL1349, Lauroglycol 90, Plurol Oleique CC 497, Labrasol and Transcutol-P were gift samples received from Gattefosse Pvt. Ltd. (Mumbai, India). Tween 80 and Sorbitol sesquioleate were purchased from Sigma-Aldrich (Bangalore, India). BO was purchased from Gaushala (cow shelter), Wardha. All other chemicals and reagents were of analytical reagent grade and were used without further purification.

2.2. Method

2.2.1. Spectrophotometric determination

A primary stock solution of QF was prepared in phosphate buffer for carrying out permeability study, *in-vitro* release study and in methanol for estimation of drug solubility in various vehicles to achieve a final concentration of 1000 mg/ml. This solution was scanned against methanol as blank in the range of 200–400 nm using UV-visible (UV-Vis) spectrophotometer (Shimadzu 1800, Tokyo, Japan) to determine λ_{max} values. Calibration curve of QF was plotted in the concentration range of 5–30 μg/ml for Phosphate buffer saline pH 6.4 and 2–12 μg/ml for methanol.

2.2.2. High-performance liquid chromatography analysis

Analytical and bioanalytical method for QF was developed and validated for quantification of QF using HPLC. The developed method was used to estimate drug concentration reaching the rat's brain, plasma and retaining in nasal mucosa during the *in-vivo* study. QF was analyzed using high-performance liquid chromatography system (HPLC) LC-2010C HT (Shimadzu, Japan) which consisted of UV/VIS detector and Labsolutions chromatographic software. A reverse phase C18 column (250 × 4.6 mm, 5 μ, kinetex, Phenomenex, USA) was used at room temperature. A mixture of