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Research paper

Enhanced solubility and dissolution of curcumin by a hydrophilic polymer solid dispersion and its *insilico* molecular modeling studies

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ABSTRACT

Curcumin (CUR) is highly lipophilic drug that shows degradation at alkaline pH which restricts its oral bioavailability. The aim of the present study was to enhance the oral bioavailability of CUR by increasing its solubility and dissolution rate. Solid dispersions (SDs) of CUR in aqueous and organic solvent using Eudragit EPO (EuD) were prepared by spray drying and rota evaporation technique. The solubility of plain CUR in acidic pH 1.2 is only 0.02% whereas SDs containing EuD have solubilities of 40.29% and 18.78% by spray drying and rota evaporation technique respectively. Physical characterization by SEM, IR, DSC, and XRD studies, revealed the changes in solid state during the formation of dispersion and justified the decreased crystallinity of CUR SDs. Dissolution studies showed that pH values influenced the release profile lower the pH values higher the release speed (pH 1.2). CUR in pH 1.2 showed negligible release even after 120 min (2–5%) whereas, SDs showed 20–45% drug release after 60 min. Further, *insilico* docking study was carried out followed by molecular dynamic simulations to understand the molecular level binding interactions between drug and polymer. The *insilico* studies demonstrates the role of van der Waals interactions in binding of CUR to EuD.

1. Introduction

Curcumin (CUR) [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione] is a naturally occurring hydrophobic polyphenol extracted from the plants of the *Curcuma longa*, its structure was showed in (Fig. 1) [27].

It has variety of biological activities and pharmacological actions, such as anticancer, antiviral, antiarthritic, antiamyloid, antioxidant and anti-inflammatory properties [8]. In spite of these wide span of activities of CUR, its therapeutic efficiency has been highly limited due to poor solubility in water (the maximum solubility was reported to be 11 ng/ml in plain aqueous buffer pH 5.0) [11]. Low bioavailability of CUR after oral delivery in addition to poor aqueous solubility, is attributed to high pre-systemic metabolism in gastrointestinal tract (GIT), degradation in GIT at neutral and alkaline pH, rapid systemic metabolism to sulfate and glucuronide conjugates leading to short half-life [4,34].

Different strategies were used to overcome these problems include conversion of CUR to amorphous microparticles by improving its solubility in acidic pH and improving CUR stability in aqueous media [28]. Numerous formulation approaches have been made to design soluble formulation of CUR, which include loading CUR into liposome or nanoparticle, self-emulsifying drug delivery system (SMEDDS) and CUR cyclodextrins complexation [26]. However, slow process of complexation, high molecular weight of cyclodextrins and pH of the processing medium may limit their practical utility. Different hydrophilic polymers such as PVP K-30, PEG 4000 and PEG 6000 have been tried for solubility and dissolution rate enhancement of CUR by different solid dispersion (SDs) techniques [2,28]. The hydrophilic polymers used in this study was Eudragit EPO (EuD). EuD which is a cationic copolymer with dimethyl-amino ethyl methacrylate as a functional group. The polymer has a maximum solubility in gastric fluids up to pH 5.

Spray drying is a technique used for development of microparticulate SDs for improving the stability and solubility of compounds [6,33]. Spray drying technique gives uniform and spherical shape particles that are small in size and that have narrow

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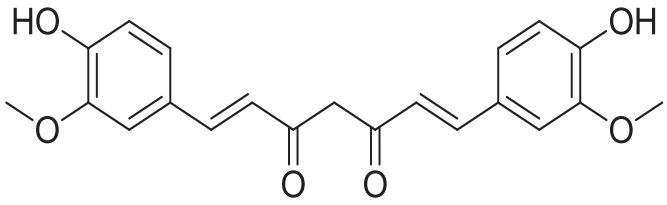

Fig. 1. The structure of curcumin.

distributions. Spray drying technique is used in the food industry due to its high productivity, its relatively low cost of production, the increased microbiological stability of phytopharmaceutical products and decreases the risk of chemical and/or biological degradations [25]. Spray drying has been used to produce biopharmaceuticals and biomaterial products [32].

Cationic polymer (EuD) based SDs by using scalable spray drying and rota evaporation techniques are the appropriate option for solubility enhancement of CUR. The present work examines the influence of hydrophilic polymer EuD on solubility and dissolution rate of CUR followed by *insilico* prediction of the interactions between the drug and polymer to understand the possible mechanism of binding and enhancement of solubility and dissolution rate of CUR. The work also involved studying the effect of method of preparation of SDs on the dissolution rate of CUR.

2. Materials and methods

2.1. Materials

CUR was obtained as a gift sample from K. Patel Phytoextratct Ltd. (Mumbai, India). EuD (Eudragit EPO) from Evonik industries Ltd. (Mumbai India) was used as the hydrophilic carrier soluble at gastric fluid pH 5. Methocel® E5-LV and Cremophore RH 40 were obtained from Dow Chemical's (Mumbai, India), and BASF India respectively. Tween 80 from SD Fine Chemicals Ltd. as surfactant. Cross carmellose sodium was obtained as gift sample from Anshul Life Sciences Ltd., Avicel PH 101 and lactose was procured from Signet Chemicals Ltd. Mumbai. Solvent selected for solubilization of CUR was acetone (RANKEM AR grade), absolute ethanol (AR grade) and distilled water. All other reagents used were of analytical reagent grade.

2.2. Physical mixture (PM)

The physical mixtures (PM) of drug with polymer EuD were prepared by simple blending of CUR50% with the hydrophilic polymer 49% and HPMC E5 1%. The blends obtained were passed through a sieve value of 250 micron size.

2.3. Preparation of spray dried microspheres

2.3.1. Solid dispersion preparations

The composition of prepared formulations were depicted in (Table 1). SDs were prepared by different methods to enhance solubility of CUR in acidic medium using the pH dependent polymer EuD.

The CUR-EuD SDs were prepared by spray drying and rota evaporation technique.

2.3.2. Using organic solvent

A CUR SDs using organic solvent were obtained by dissolving a weighed quantity active, EuD and HPMC E5 in ethanol/acetone and dried using spray dryer (CUR01 & CUR02) (Jay Instruments and Systems Pvt. Ltd., India) and Rota Evaporator (CUR04 & CUR05) (Heidolph, Lab rota Efficient 400 WB eco, India).

The operating parameters for spray drying were: inlet temperature 54–56 °C; outlet temperature 42–45 °C; feed rate 2–5 ml/min; atomization air pressure 2–3 kg/cm^2; and aspiration rate40–45%.

For, rota evaporator drying temperature was set to 60 °C.

2.3.3. Using aqueous solvent

A CUR SDs using aqueous solvent was obtained by preparing o/w emulsion of CUR (CUR03) using Cremophore RH 40 as oil, HPMC E5 as recrystallization inhibitor and Tween 80 as solubilizer and further spray dried. The operating parameters were: inlet temperature 105–110 °C; outlet temperature 55–60 °C; feed rate 1–5 ml/min; atomization air pressure 2–3 kg/cm^2 and aspiration rate40-45%.

2.4. Standard curve of CUR in 0.1N HCl and in different pH medium

The standard curve of CUR was prepared in different pH medium (pH 1.2/pH 4.5, pH 6.8 and pH 7.8). A 1000 μg/ml stock solution of CUR was prepared in with addition of 10 ml of glacial acetic acid. From this stock solution, 1 ml aliquot was withdrawn to prepare a 10 μg/ml solution of CUR in different pH medium. The 10 μg/ml solution of CUR was diluted suitably to 10 ml each medium to obtain respective concentrations of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 μg/ml of CUR. The absorbance of these solutions was recorded at 420 nm on a Shimadzu UV Spectrophotometer (UV – 1650 PC). The absorbance versus concentration data ($n = 3$) was treated by least squares linear regression analysis.

2.5. Drug content analysis

10 mg of the sample was weighed accurately and dissolved in 10 ml glacial acetic acid (AR). The solution was sonicated for 10 min and the sample was centrifuged at 10,000 rpm for 5 min. The supernatant was diluted with suitable quantity of methanol. The absorbance of supernatant solution was recorded at 420 nm using

Table 1
Formulation composition of CURSDs.

Formulation %	CUR01 (Rota Evap.)	CUR02 (Spray drying)	CUR03 (Spray drying)	CUR04 (Rota evap.)	CUR05 (Spray drying)
CUR	50	50	50	50	45
Eudragit EPO	49	49	40	49	49
HPMC E5	1	1	1	1	1
Cremophore RH 40	–	–	12	–	–
Tween 80	–	–	2	–	–
Acetone	–	–	–	q.s.	q.s.
Ethanol	q.s.	q.s	–	–	–
Purified water	–	–	q.s.	–	–