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Bioavailability Enhancement of Poorly Water Soluble and Weakly Acidic New Chemical Entity with 2-Hydroxy Propyl-β-Cyclodextrin: Selection of Meglumine, a Polyhydroxy Base, as a Novel Ternary Component

S. Basavaraj, Vaibhav Sihorkar, T.R. Shantha Kumar, Prakash Sundaramurthi, and Nuggehally R. Srinivas
Formulation Research Department, Discovery Research, Dr. Reddy's Laboratories Ltd., Hyderabad, India

P. Venkatesh, Mullangi Ramesh, and Nuggehally R. Srinivas
Drug Metabolism and Pharmacokinetic Department, Discovery Research, Dr. Reddy's Laboratories Ltd., Hyderabad, India

Sunil Kumar Singh
Medicinal Chemistry, Discovery Research, Dr. Reddy's Laboratories Ltd., Hyderabad, India

Nuggehally R. Srinivas
Drug Development, Discovery Research, Dr. Reddy's Laboratories Ltd., Hyderabad, India

The purpose of the present study was to investigate the influence of a polyhydroxy base, N-acetyl glucamine (also know as Meglumine), as a ternary component on the complexation of DRF-4367, a poorly water-soluble and weakly acidic anti-inflammatory molecule, with 2-hydroxypropyl-β-cyclodextrin (HPβCD). The molecular inclusion of DRF-4367 with HPβCD alone and in combination with ternary component was aimed at improvement in solubility and, subsequently, dissolution rate-limited oral bioavailability. The solid complexes of DRF-4367 and HPβCD with or without meglumine (binary and ternary systems, respectively) were prepared as coevaporated product in different stoichiometric ratios and compared against physical mixture. The formation of inclusion complexes was confirmed by using classical instrumental techniques. Phase solubility studies suggested that meglumine was responsible for solubility improvement via multiple factors rather than just providing a favorable pH. Mechanisms and factors governing solubility enhancement were investigated by using phase solubility and thermodynamic parameters. The complexation of DRF-4367 with HPβCD is thermodynamically favored because the Gibbs free energies of transfer of the drug to the cyclodextrin cavity are negative. The solubilization efficiency and stability were further improved while retaining the favorable Gibbs free energies of transfer with the addition of meglumine. Inclusion ternary complex of DRF-4367 with HPβCD and meglumine showed significant improvement in dissolution compared with uncomplexed drug and binary system. Moreover, the phenomena of reprecipitation observed with binary system during dissolution could be avoided with meglumine as an enabling ternary component. This improved physicochemical behavior of ternary complex with the novel inclusion of a polyhydroxy base translated into an enhanced oral bioavailability of DRF-4367 compared with either uncomplexed drug or nanosuspension.

Keywords DRF-4367, 2-hydroxypropyl-β-cyclodextrin, ternary component, polyhydroxy base, meglumine, solubilization, new chemical entity

INTRODUCTION

The advent of combinatorial and high-throughput screening technologies has contributed to influx of lead molecules into discovery pipeline phenomenally. It is estimated that about 40% of molecules entering the discovery pipeline fail because of poor solubility or permeability,[1,2] the two important parameters that influence the viability of lead molecules in drug development. Many of the pipeline molecules are highly lipophilic and possess poor aqueous

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Address correspondence to Dr. Nuggehally R. Srinivas, Executive Vice President, Drug Development, Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad, India 500 049; Tel: +91 40 2304 5439 ext. 414; Fax: +91 40 2304 5438; E-mail: nrsrinivas@drreddys.com

solubility; in most cases they lead to dissolution rate limited bioavailability issues.[3]

DRF-4367 is chemically, 2-hydroxymethyl-4-[5-(4-methoxyphenyl-3-trifluromethyl-1H-1-pyrazolyl] -1-benzenesulphanamide (Figure 1). It is a cyclooxygenase-2 (COX-2) specific new chemical entity (NCE) with nonsteroidal anti-inflammatory activity and is intended to relieve pain and inflammation. It is practically insoluble in water and in other physiologically relevant buffers.[4] Oral pharmacokinetics (PK) studies in rats with suspension formulation of DRF-4367 showed bioavailability of 20% and 40% at doses of 100 and 30 mg/kg, respectively.[5] This nonlinear dose-dependent phenomenon observed in oral PK studies could be attributed to poor solubility/dissolution in gastrointestinal fluid. Attempts with conventional solubilization approaches, such as pH adjustment, cosolvent, and surfactant addition, could not improve the solubility of DRF-4367. Therefore, further development of DRF-4367 required identification and characterization of formulation strategy to improve dissolution and bioavailability for peroral and/or *IV* administration.

Cyclodextrins (CDs) have received increasing attention in pharmaceutical field because of their ability to enhance solubility, stability, and bioavailability through the formation of inclusion complexes.[6,7] However, it is imperative that pharmaceutical dosage form should contain appropriate and approved amount of CDs, because use of excess amounts of CDs may lead to potential toxicity and other related side effects, which may impede its use in drug development.[8] Hence, optimization of complexation process and possibility to explore multicomponent systems to gauge the cyclodextrin concentration within permissible limits and further improve efficiency in terms of dissolution and bioavailability were mandated. In this context, the influence of additional (ternary) components in enhancing cyclodextrin solubilization of poorly water-soluble drug has received research focus and momentum over the years.

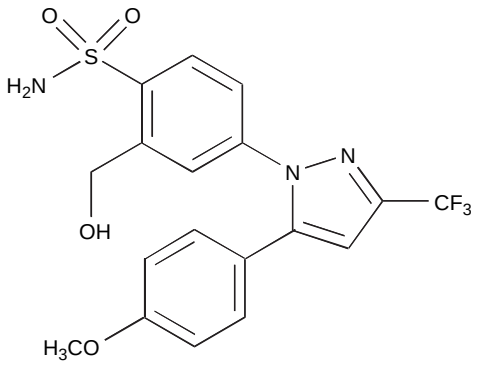


Figure 1. Structure of DRF-4367.

Recent reports suggest the application of simultaneous salt formation and CD complexation for improving pharmaceutical performance of weakly basic and acidic drugs.[9,10] Effect of pH on complexation of itraconazole with HPβCD revealed varying order of complexation and solubilizing power at different pH values.[11] Mesylate salt of ziprasidone has been used with sulfaobutylether cyclodextrin in developing an intravenous formulation.[12] Many researches have also reported the use of water-soluble polymers for enhancing complexation efficiency.[13,14] However, efforts like simultaneous salt formation and complexation may pose challenges due to lack of stability of complexation. This may lead to supersaturation and finally reprecipitation at physiologically relevant pH conditions. Therefore, solubilization of DRF-4367 using cyclodextrin and in situ salt formation with basic counterion can pose a problem of reprecipitation at gastric pH, hence, selection of suitable counterion (ternary component), which can hold complex intact at various physiological conditions, was desired.

Therefore, it seemed worthy of interest to evaluate N-acetyl glucamine (also known as meglumine), a polyhydroxy organic amine (base), as a novel ternary component to enhance complexation of weakly acidic DRF-4367 with HPβCD. The studies were aimed at improvement of complexation efficiency and stability at physiologically relevant pH. The phase solubility studies and thermodynamic parameters were extensively used to select ternary component and to postulate mechanisms underlying the stable ternary complex formation and solubility enhancement. These multicomponent complexes were further assessed for enhancement in dissolution and subsequent translation on oral bioavailability using pharmacokinetic studies in Wister rats.

MATERIALS AND METHODS

Materials

DRF-4367 was synthesized by Discovery Chemistry, Dr. Reddy's Laboratories Ltd. (DRL), Hyderabad, India, and was characterized by using chromatographic and spectral techniques. Purity was found to be 99%. 2-Hydroxylpropyl-β-cyclodextrin (HPβCD, Pharma grade, W7 HP PHARMA) with an average molecular weight (MW) of 1400 daltons and a molar substitution of 0.58–0.73 was procured from Wacker-Chemie GmbH, Germany. N-methyl-D-glucamine (meglumine) was purchased from Lancaster, England. Ethanol and other solvents used were of HPLC grade; other chemicals used were of analytical grade.

Phase Solubility Studies and Determination of Binding Constant

The phase solubility experiment was performed by the method reported by Higuchi and Connors.[15] In brief, an excess amount of DRF-4367 in purified water containing various concentrations of HPβCD (0–30% w/v) was shaken for 24 hr at controlled room temperature (25 ± 1°C), 40 ± 1°C, and 45 ± 1°C) on a shaker water bath rotating at 200 rpm (Julabo, USA). The equilibrated aliquots were filtered through 0.22-μm PVDF filter (Millipore, India) followed by dilution with methanol and analyzed spectrophotometrically at 243 nm (Beckman, USA). UV spectroscopy was also run for pure cyclodextrin and meglumine solutions of similar concentrations and no interference could be detected at λmax of DRF-4367. Similar phase solubility experiments were also conducted with DRF-4367 in HPβCD solutions containing various concentrations of meglumine (0–1.0% w/v) and also vials containing DRF-4367 in HPβCD solutions prepared by using glycine/NaOH buffers (pH 10.2). The pH of equilibrated solutions was measured by using a pH meter (Orion, Cambridge, MA). The thermodynamic parameters and apparent binding constant were calculated by using mathematical equations.[15]

Preparation of Solid Complexes

The solid complexes of DRF-4367 and HPβCD with or without meglumine were prepared by the following techniques. The stoichiometric ratio of binary system was kept as 1:1 and 1:2, whereas that of ternary systems was kept as 1:1:1 and 1:2:1. Prepared complexes were characterized by using DSC and XRD.

Physical Mixture

The physical mixtures were prepared by gently mixing previously pulverized powders of DRF-4367, HPβCD, and meglumine. These mixtures were passed through an 80-mesh sieve prior to use. A similar experiment was performed without meglumine.

Coevaporation

Accurately weighed DRF-4367, meglumine, and HPβCD were dissolved in ethanol and stirred well at 70°C until the solution was clear. This solution was evaporated at 70°C by using a rotary evaporator (Laborota 4001, Heidolph, Germany). The solid residue (coevaporated product) was further dried under high vacuum for 24 hr. Similarly, solid complexes were prepared without meglumine.

Characterization of the Complex

Differential Scanning Calorimetry

Thermal characteristics of native DRF-4367 and its complexes were analyzed under dry nitrogen purge (50 mL/min) at a heating rate of 5°C/min using a Differential Scanning Calorimeter (DSC 50, Shimadzu, Japan) operated with DSC-50 software.

Powder X-ray Diffractometry

X-ray powder diffraction pattern of native DRF-4367 and its solid complexes were recorded at room temperature by a diffractometer (Rigaku 227, Denki, Tokyo, Japan) using a scintillation counter. Powder was grounded slightly before subjecting to XRD analysis.[16]

Solubility Studies

The solid binary (1:2) and ternary complex (1:2:1) complexes made from coevaporation technique (equivalent to 5 mg of DRF-4367) were taken in 1 mL of MQ water and physiological buffers of pH 1.2 and 6.8 and shaken for 1 min and observed for clarity.

Dissolution Rate Studies

The in vitro dissolution studies of pure DRF-4367, physical mixture of DRF-4367, HPβCD and meglumine, and solid complexes were carried out by using USP type II apparatus (Electrolab, India). Sample equivalent to 25 mg of DRF-4367 was taken in 900 mL of water maintained at 37°C ± 0.2°C and stirred at 50 rpm. Samples were withdrawn at 5-, 10-, 15-, and 30-min interval, filtered through 0.22-μm PVDF filter (Millipore, India), diluted appropriately with methanol, and analyzed for DRF-4367 spectrophotometrically.

Single-Dose Pharmacokinetic Study

The pharmacokinetic evaluation of DRF-4367 in a conventional suspension formulation (0.25% w/v NaCMC), nanosuspension and ternary cyclodextrin complex prepared by coevaporation was performed in male Wistar rats. Institutional animal ethics committee approved the study protocol. A single dose of 100 mg/kg of DRF-4367 was given per orally to rats (fasted overnight) and 10 mg/kg for intravenous PK studies. Blood samples were collected from the retro orbital plexus at 0.5, 1, 2, 3, 5, 8, 12, and 24 hr for oral and 0.17, 0.5, 1, 2, 4, 6, 8, 12, and 24 hr

for intravenous administration to tubes containing 2.0% EDTA (50 μL) as the anticoagulant.

Collected samples were processed and stored at −20°C until analysis. A 100-μL aliquot of plasma was mixed with 10 μL of methanolic celecoxib (internal standard). To this, 2 mL of dichloromethane was added and vortexed for 2 min, and solvent was evaporated at 50°C to dryness. The residue so obtained was reconstituted in mobile phase. Validated HPLC-UV method was used for the analysis of plasma samples.[5] Briefly, this method uses 4.6 × 250 mm Kromasil (KR 100–5C-18–6695A) analytical column for separation of analyte. The mobile phase used was 0.05 M sodium dihydrogen orthophosphate buffer (pH 3.2) and acetonitrile mixture (40:60 v/v); celecoxib (1 μg/100 μL of plasma) was used as an internal standard. Plasma concentrations vs. time profile was generated and subjected to noncompartmental pharmacokinetic analysis to calculate PK parameters (C_{max}, T_{max}, K_{el}, Cl, and F) with WINNONLIN software. A single intravenous bolus was given at a dose of 10 mg/kg to calculate the absolute bioavailability (*F*) by using the following equation.

$$F = \left[\frac{Dose(IV) \times AUC_{(0-\infty)\ Oral}}{Dose(Oral) \times AUC_{(0-\infty)IV}} \right] \times 100$$

Statistical significance of the pharmacokinetic parameters was evaluated by one-way ANOVA at 95% confidence interval.

RESULTS AND DISCUSSION

Phase Solubility Studies

The phase solubility studies at three different temperatures (25°C, 40°C, and 45°C) in binary and ternary systems with HPβCD and meglumine, respectively, were performed to understand drug solubilization mechanism of multicomponent complex formation. Phase solubility diagram is shown in Figure 2. In all the cases, aqueous solubility of DRF-4367 increased linearly as the function of concentration of HPβCD with the slope less than unity, signifying the formation of 1:1 soluble complex, AL type, as described by Higuchi and Connors.[15]

DRF-4367 is a weakly acidic NCE with a predicted pKa of 8.86 (sulfonamide group). Initial solubility (S_0) in water is 2.55 μg/mL; however, with 0.25% and 1% meglumine, the solubility increases to 21.5 (~10-fold) and 60 μg/mL (~25-fold), respectively. Solubility of DRF-4367 in HPβCD was increased in the presence of meglumine as shown in phase solubility diagram (Figure 2). The

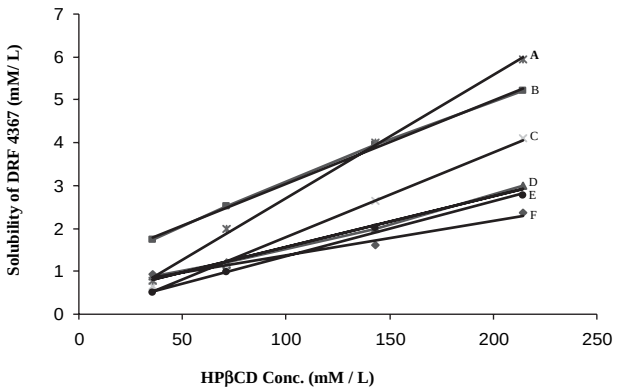


Figure 2. Phase solubility studies: A, solubility of DRF-4367 with HPβCD and 0.25% w/v meglumine at 40°C; B, solubility of DRF-4367 with HPβCD and 1% w/v meglumine at 25°C; C, solubility of DRF-4367 with HPβCD alone at 40°C; D, solubility of DRF-4367 with HPβCD and 0.25% w/v meglumine at 25°C; E, solubility of DRF-4367 with HPβCD alone at pH 10.2; and F, solubility of DRF-4367 with HPβCD alone at 25°C.

ratio between the slopes of solubility curves of ternary to binary is assumed to be the index of relative solubilizing efficiency,[9] which was recorded to be 1.5 and 2.5 with 0.25% w/v and 1% w/v of meglumine, respectively, thus confirming the greater effectiveness of ternary system.

Interestingly, we noted a 10-fold decrease in binding constant observed in the ternary system, compared with the binary system (Table 1). This decrease in affinity toward cyclodextrin cavity in the presence of the counterion can be explained on the basis of higher initial aqueous solubility of DRF-4367 as a result of ionization.[17] However, this effect was counterbalanced by an overall increase in solubility of about 900-fold with ternary system (1% w/v meglumine-based ternary complex), compared to about 400-fold with HPβCD binary system.

Meglumine is a polyhydroxy organic amine having a pKa of 9.5 and a pH of 10.1 of a 1% w/v solution. It was initially hypothesized that a higher pH would result in ionization and, hence, improved complexation with HPβCD. To test this hypothesis, phase solubility studies were carried out with glycine/NaOH buffer (pH 10.2). This was done to understand whether observed improvement in complexation and hence solubilization (offered by meglumine) is merely due to ionization (pH effect) or multiple factors contributed by ternary component. The results of phase solubility with Glycine/NaOH buffer (pH 10.2) clearly showed that there was no significant advantage of pH effect in solubility over HPβCD alone. The reason behind the improvement of complexation with meglumine can be explained on the basis of multiple factors, including simultaneous in situ salt formation and spatial configuration contributed by component.[18]

Table 1
Effect of meglumine on solubilizing efficiency, stability constants, and thermodynamic parameters of DRF-4367

	Solubilization efficiency[a]	Binding constant (M^{-1})			Thermodynamic properties		
		25°C	40°C	45°C	ΔG KCal M^{-1}	ΔH KCal M^{-1}	ΔS Cal $M^{-1}K^{-1}$
HPβCD alone	400	1549.9	1771.9	1633.9	–4.35	0.465	16.15
HPβCD + 0.25% w/v meglumine	488	221.12	176.9	162.5	–3.19	–1.22	6.62
HPβCD + 1% w/v meglumine	888	122.76	ND	ND	ND	ND	ND

[a]Ratio of solubility of DRF-4367 in water to solubility of DRF-4367 at 30% (214 mM/L) of HPβCD.
ND = Not done.

Pose-Vilarnovo and coworkers[19] found that the addition of a base like ammonium hydroxide to sulfaonamides resulted in an enhanced cyclodextrin complexation. Therefore, selection of a particular component in ternary system was pivotal to help maintain solubility and stability of complex in physiological pH range. Because meglumine is a polyhydroxy amine, the OH groups may involve in hydrogen bonding with the host and at a lower pH, the complex is held intact. Although drug tends to become unionized at lower pH, it is tightly bound in cavity because of ternary complex and hydrogen bonding of meglumine with host. Thus, the ternary complex may provide multiple mechanisms to promote both solubility and stability.

To evaluate the contribution of thermodynamic parameters, solubility of DRF-4367 in HPβCD was also studied at 40°C and 45°C and compared with that at 25°C. Various thermodynamic parameters such as ΔG, ΔH, and ΔS were calculated (Table 1). Higher negative ΔG observed in both binary and ternary systems could be attributed to complex formation and mainly depends on structural compatibility between guest and host.[20] The observation of positive ΔH and higher positive ΔS in DRF-4367 and HPβCD binary system are indicative of classical hydrophobic and endothermic interactions, which are mainly involved in transfer of guest molecule into cavity and breakdown of water structure around the guest.[21,22] Positive ΔH observed with HPβCD can be attributed to the transfer of DRF-4367 from aqueous medium to more apolar site of cyclodextrin cavity. This transfer may get associated with breakdown of water structure around molecule, which probably leads to higher positive ΔS.

Negative ΔH observed in the presence of meglumine (ternary system) indicates that complexation process is an exothermic process. Negative ΔH may be due to release of enthalpy-rich water molecule as a result of ternary complex formation. Moreover, because of close packing of DRF-4367 and meglumine in single cavity, distance between guest and cavity becomes small and strong exothermic van der Walls-London dispersion forces might be associated with ternary complex formation. This leads to an enthalpy of complexation and because meglumine is polyhydroxyamine, hydrogen bonding with host is possible. Slight positive entropy in ternary systems may be due to perfect snug fit of DRF-4367 and meglumine in single cavity of CD. Structural restraint could cause movements of α-1, 4-glycosidic linkages to be restricted as a result of ternary system formation, thereby stabilizing the ternary system.[20,21]

Considering all above facts, it can be hypothesized that multiple factors contribute to the ternary complex formation, and specific interaction of meglumine with sulfanamide group of DRF-4367 and hydrogen bonding with the host could be cited as probable reasons for improvement in complexation efficiency and solubilization.

Characterization of Solid Complexes

Differential Scanning Calorimetry

Thermal behavior of DRF-4367 and its solid complexes along with its individual components are shown in Figures 3 and 4. As depicted in Figure 3, DRF-4367 showed a sharp endotherm at 189°C attributed to melting, whereas HPβCD showed a broad endotherm from 65°C to 100°C, which could be attributed to the loss of moisture. Being highly crystalline, meglumine showed a sharp melting peak at 129°C.

Thermograms of the solid complex prepared by physical mixture showed a peak at 127°C and an endothermic peak at 169°C, which could be correspondingly attributed to the melting of meglumine and DRF-4367. Lower shift in melting point of DRF-4367 is attributed to the presence of binary mixture, as the melting point of a material is known to shift to the lower scale in the presence of other substances.[23] On the contrary, the thermograms of solid complexes prepared by coevaporation are different from that of physical mixture and pure components; the melting of both DRF-4367 and meglumine were found missing, which gives a clear premise that there is formation of solid ternary complexes.

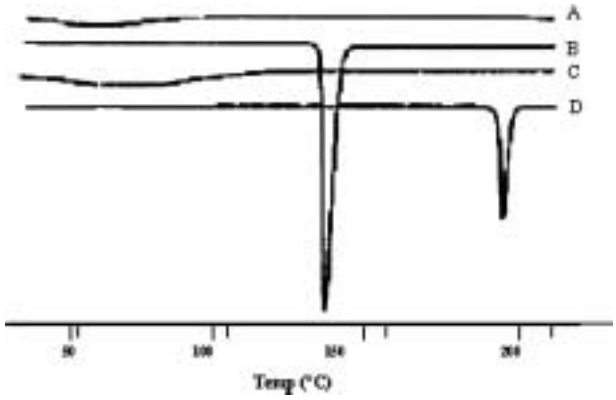


Figure 3. DSC thermograms of native DRF-4367 and its complexes: A, DRF-4367 HPβCD (1:1:1) complex in presence of meglumine (coevaporated product); B, meglumine; C, HPβCD; and D, DRF-4367.

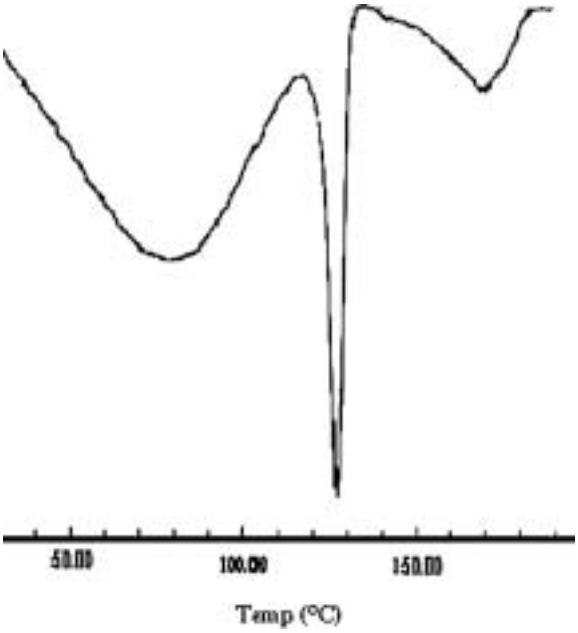


Figure 4. DSC thermograms of DRF-4367-HPβCD physical mixture.

Powder X-ray Diffractometry

The pXRD patterns of native DRF-4367 and solid complexes prepared by coevaporation process (coevaporated product) are presented in Figure 5. The diffractograms of DRF-4367 and meglumine exhibited a series of intense peaks, which are indicative of their crystalline character. The pXRD of HPβCD showed a broad amorphous halo, indicating absence of crystalline state. An X-ray diffraction pattern of physical mixture was constituted by some of the characteristic peaks of DRF-4367, indicating an absence of stiochometric complexation. Complexes with meglumine, on the other hand, indicated a significant reduction in peak intensity (amorphonization), thus confirming the ternary complex corroborating the DSC observations.

Solubility Studies

Ternary solid complex of DRF-4367 with HPβCD and meglumine (coevaporated powder product) was found to be soluble (tested at 5 mg/mL) in MQ water and in physiological buffer solutions, and no precipitation was recorded until 30 min at controlled room temperature. On the other hand, in binary systems, the solubilization was followed by rapid precipitation within a few minutes of preparation. This finding substantiates the role and impact of meglumine as a suitable ternary component for multicomponent complexation of DRF-4367 with HPβCD.

Dissolution Studies

Dissolution profiles of various solid complexes of DRF-4367 (physical mixture and coevaporated products) are shown in Figure 6. Dissolution studies of DRF-4367 alone in MQ water showed no detectable quantity. DRF-4367-HPβCD binary complex (1:1 stoichiometric ratio) prepared by coevaporation showed significant improvement in dissolution, >80% after 30 min but slight reprecipitation was observed. To prevent precipitation, HPβCD was increased to 2 mole equivalent (1:2 stoichiometric ratio). This has delayed the reprecipitation but could not abolish it. The precipitation or recrystallization of DRF-4367 in same or different solid phase may have a bearing on the biological fate of the molecule after administration in vivo. As shown in the Figure 6, the dissolution profiles of solid complexes of DRF-4367 with HPβCD in the presence of meglumine showed improved dissolution rate. Ternary complex (DRF-4367-HPβCD-meglumine) showed >90% dissolution after 30 min, and no precipitation could be observed.

Pharmacokinetic Studies

Pharmacokinetic studies were performed with ternary inclusion complexes, and results were compared with suspension and nanosuspension. Because of its poor solubility, DRF-4367 may be a candidate of dissolution rate-limited bioavailability. Nanosuspension formulation of DRF-4367 was included in the study to gauge the possibility of bioavailability enhancement due to reduction in particle size compared against solubilization offered by ternary complex formation. The mean log plasma concentration

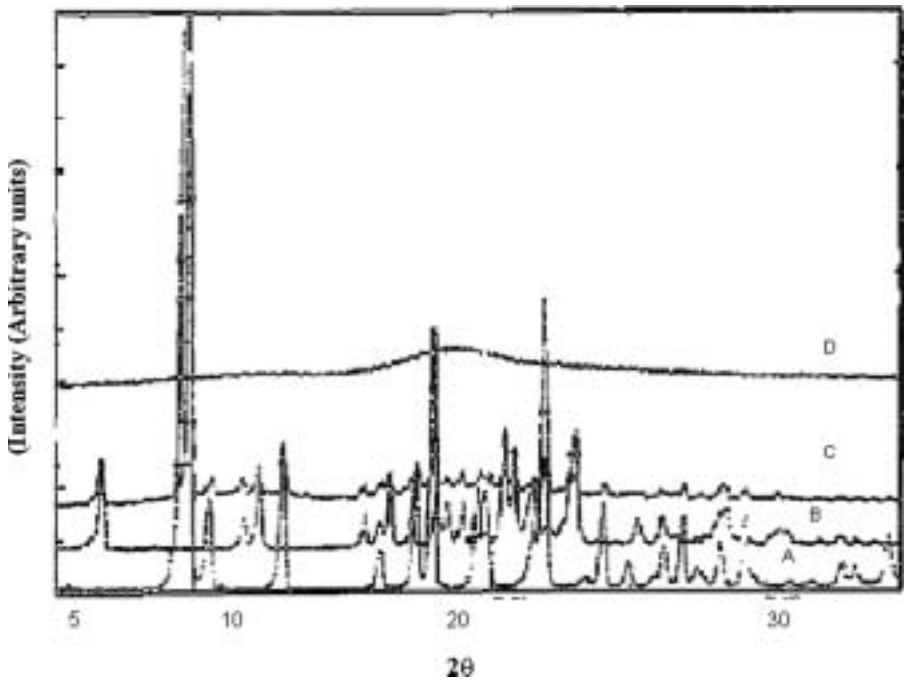
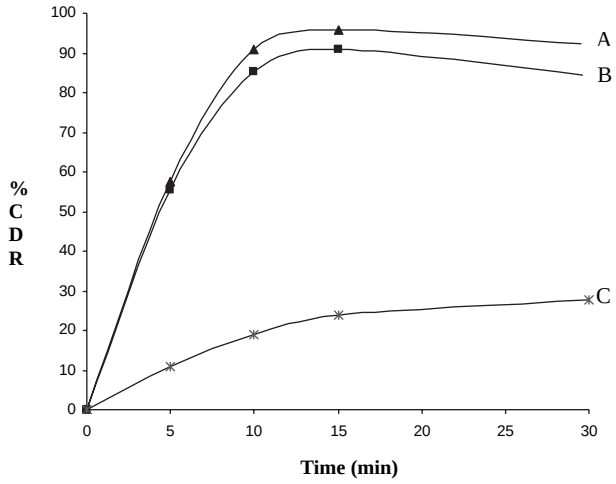


Figure 5. Powder XRD patterns of DRF-4367 and its complexes; A, meglumine; B, DRF-4367; C, physical mixture; D, DRF-4367 HPβCD complex with meglumine (1:1:1) (coevaporated product).



% CDR: % Cumulative Drug Release

Figure 6. Dissolution profile DRF-4367 and its complexes: A, Dissolution profile of DRF-4367-HPβCD-meglumine (1:2:1) (coevaporated product); B, dissolution profile of DRF-4367-HPβCD (1:2) (coevaporated product); C, dissolution profile of physical mixture of DRF-4367-HPβCD-meglumine (1:2:1).

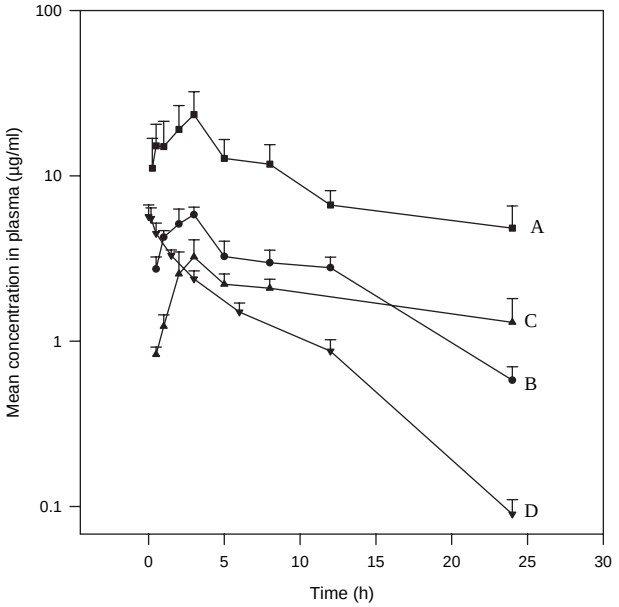


Figure 7. Pharmacokinetic profile of different formulations of DRF-4367: A, Ternary complex solution (100 mg/kg) p.o; B, nanosuspension (100 mg/kg) p.o; C, NaCMC suspension (100 mg/kg) p.o; D, intravenous solution (10 mg/kg).

vs. time profile of DRF-4367 on single per oral and intravenous administration to male Wistar rats is shown in Figure 7. The mean oral PK parameters are summarized in Table 2. DRF-4367 was well absorbed, reaching maximum plasma concentration with in 3.4 hr, whereas in solution it appeared somewhat earlier (2.75 hr). Similarly,

Table 2
Oral pharmacokinetic parameters of DRF-4367 on administration of various formulations in Wister rats

Formulation	$AUC_{(0-\infty)}$ (μg*hr/mL)	C_{max} (μg/mL)	t_{max} (hr)	$K_{el}(hr^{-1})$	$t_{1/2}$ (hr)
Ternary complex solution (10 mg/mL)[a]	295.69 ± 41.58	23.66 ± 8.41	2.75 ± 0.58	0.08 ± 0.06	10.6 ± 6.08
Nanosuspension (10 mg/mL)	69.00 ± 8.13	5.90 ± 0.58	3.40 ± 1.52	0.10 ± 0.02	7.36 ± 1.67
Suspension (10 mg/mL)	57.42 ± 12.62	4.08 ± 1.08	3.67 ± 0.98	0.08 ± 0.02	9.33 ± 3.05
IV (1 mg/mL)[b]	28.05 ± 4.13	-	-	-	6.7 ± 0.56

[a]Dose (100 mg/kg); [b] Dose (10 mg/kg).

there was no statistical (*t*-test) significant difference ($p > 0.05$) in $t_{1/2}$ of DRF-4367 on administration of different formulations.

Absolute oral bioavailability of DRF-4367 from ternary complex solution, nanosuspension and conventional NaCMC suspension were determined to be 100, 25, and 20%, respectively. Mamidi and coworkers reported similar absorption-related issues in celecoxib and its analogs, due to lack of solubility in the gastrointestinal tract at relatively higher doses.[24] Ramesh and coworkers (2003) studied the oral pharmacokinetics of DRF-4367 in the dose range of 2–100 mg/kg in rats and reported that bioavailability decreased with increase in the dose.[5] These workers could achieve maximum bioavailability of 70% at the lowest dose of 2 mg/kg. The bioavailability was reduced in the subsequent higher doses. Therefore, the observed enhancement in absolute oral bioavailability of DRF-4367 using ternary complex-based solution formulation at higher dose was very important to support further development of this NCE. Overall, the use of HPβCD-meglumine multicomponent complexation enhances solubility of DRF-4367 under varied gastrointestinal conditions and translates in to an enhanced oral bioavailability. This approach may be feasible for other cyclooxygenase inhibitors and other weakly acidic drugs that display dissolution-limited bioavailability issues.

CONCLUSION

This study demonstrated the possibility of significantly improving the dissolution rate-limited bioavailability of weakly acidic molecules by using polyhydroxy organic amine (base) as a suitable ternary component. The importance of proper selection and optimization of most suitable component to adequately improve solubility, complexation efficiency, and stability under various physiological pH conditions, has been addressed by using meglumine-DRF-4367-HPβCD ternary complex. The improvement in solubility and dissolution unequivocally translated into an enhanced oral bioavailability of DRF-4367. Meglumine as a component seems to be contributing by a combination of multiple factors and probably offers ideal interaction with DRF-4367, including specific hydrogen bonding and/or spatial alignment with the host.

Hence, these systems could be useful for formulating BCS class II drugs, such as DRF-4367, as revealed by increased bioavailability in animal experiments.

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