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Research Article

FORMULATION DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF TERNARY HYDROTROPIC SOLID DISPERSIONS OF ACECLOFENAC

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ABSTRACT

Objective: Among the various strategies employed to enhance solubility, dissolution, and bioavailability of poorly soluble drugs *in vivo*, formulation of solid dispersion (SD) using hydrophilic and/or water-soluble carriers with varying physicochemical characteristics seems to be a developable, economically viable and easy option. The goal of the present study was to explore the possibilities of skimmed milk (SKM)-urea (U)-crospovidone (CP) as a novel ternary mixture of carrier-hydrotrope-superdisintegrant in SD of poorly water-soluble aceclofenac (ACF).

Methods: Compatibility of ACF and ternary mixture of SKM-U-CP was confirmed by FTIR spectroscopic analysis. SDs of ACF-SKM, ACF-SKM-U and ternary hydrotropic SD, ACF-SKM-U-CP were prepared in varying ratios of 1:1–1: 5 for ACF-SKM; 1:5:0.5, 1:5:0.75, and 1:5:1 for ACF-SKM-U and 1:5:0.75:0.25–1:5:0.75:1 for ACF-SKM-U-CP by solvent evaporation technique and were characterized by their solubility enhancement (compared to pure drug) at 25°C and drug dissolution profiles in double-distilled water and phosphate buffer (pH 6.8).

Results: Based on solubility enhancement data (82.10% and 44.06%) and maximum cumulative percentage drug release data (88.45% in 9 min and 76.18% in 60 s) in double-distilled water and phosphate buffer, respectively, ACF-SKM-U(1:5:0.75) was found to the best among ACF-SKM and ACF-SKM-U SDs which were used for studying the effect of adding CP as superdisintigrant. ACF: SKM: U: CP (1: 5: 0.75: 0.50) exhibited maximum solubility enhancement of 83.92% and 49.69% and cumulative percentage release of 98.55 % in 9 min and 85.67 % in 60 s in double-distilled water and buffer, respectively.

Conclusion: Therefore, the novel ternary mixture of SKM-U-CP has demonstrated marginal superiority over SKM as carrier for hydrotropic SDs of ACF.

Keywords: Carrier, Crospovidone, Hydrotrope, Skimmed milk, Solid dispersion, Solubility enhancement, Superdisintegrant, Ternary mixture, urea.

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INTRODUCTION

Although the oral route of administration is preferred in majority of the cases for drug delivery, it can be a problematic and inefficient mode of delivery. Limited drug absorption resulting in poor bioavailability is the most common problem that can be encountered [1-3]. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors, of which poor aqueous solubility and/or poor membrane permeability of the drug molecule play the most crucial role. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption and low bioavailability after oral administration since their bioavailability is largely dependent on the dissolution of the drug in the GI fluids [4-10].

Improvement in solubility can be achieved by the formation of solid dispersions (SD) with several hydrophilic or water-soluble substances or hydrotropes such as urea, lactose, mannitol, polyethylene glycols of various molecular weights, β-cyclodextrin, skimmed milk (SKM), HPMC, poloxamer, sodium citrate, PVP-K30, sodium starch glycolate, crospovidone (CP), croscarmellose sodium, and para-aminobenzoic acid [7,9,11-14].

SD refers to the group of solid products consisting of at least two different components, generally a hydrophilic carrier and poorly water-soluble drug [1-3,12,13]. The concept of SD was originally proposed by Sekiguchi and Obi in the early 1960s [1-3,14,15]. SD holds great promise in increasing solubility, dissolution, absorption, bioavailability, and, hence, therapeutic efficacy of poorly water-soluble drugs. In a SD, the drug is dispersed molecularly in solid state in solid carrier system. The mechanisms of enhancement of solubility and dissolution rate by employing SD include improvement in wettability and dispersibility, transformation of crystalline form of drug to its amorphous form, particle size reduction, reduction in aggregation, and agglomeration tendency of drug particles [3,5,7,15-22]. Liquid active pharmaceutical ingredients may be converted into solid formulations for ease of handling and better shelf-life [3,14,15,21,22].

Aceclofenac (ACF) is an orally effective non-steroidal anti-inflammatory drug of phenyl acetic acid group. However, it is poorly water-soluble (Biopharmaceutical Classification System Class II), due to which its dissolution in GI fluid is very low, which, in turn, adversely affects its oral bioavailability. It is reported to possess aqueous solubility of 15–103.17 µg/ml as obtained from various studies. In phosphate buffer (pH 6.8), solubility of 1058.9–1347.71 µg/ml has been reported [23-28]. Thus, attempts should be made to improve its solubility and hence dissolution rate in aqueous medium and SD by use of ternary mixture of SKM as carrier, urea as hydrotrope and CP as superdisintegrant seems to be a promising option [25-28].

SKM is readily available, cheap, and easy to handle and thus has been employed as SD carrier for solubility, dissolution, and bioavailability enhancement of poorly water-soluble drugs such as atorvastatin, simvastatin, and loratidine [3-7,11,13]. Urea has been reported to produce significant improvement in the wettability, solubility, and dissolution rate and bioavailability (in rabbits) of drugs such as olmesartan medoxomil, clarithromycin, cefuroxime axetil, and sulfathiazole [29-35]. CP is a cross-linked, water-insoluble superdisintegrant which can also be used for solubility enhancement of poorly soluble drugs, for example, SD of ondansetron hydrochloride [8,36].

No previous study has reported the use of ternary mixture of SD carrier for improvement in solubility and dissolution profile of poorly soluble drugs. The carrier components have been individually employed in several studies, but the combination has not been investigated. The use of ternary carrier mixture is expected to reduce the amount required for each component to produce desired effect. The objective of the present study is to enhance the aqueous solubility and dissolution rate of ACF by SD technique using ternary carrier mixture of SKM-urea (U)-CP as a combination of carrier-hydrotrope-superdisintegrant.

METHODS

Materials

ACF was purchased from Yarrow Chem Products (Mumbai, Maharashtra), SKM was purchased from Marvellous Overseas India Pvt Ltd (Indore, Madhya Pradesh) and U purchased from BA Chemie Pvt Ltd., (Palghar, Maharashtra), and CP was obtained as gift sample from Colorcon®. All other reagents and chemicals utilized in this study were of analytical grade.

Methods

Preparation of SDs

SDs in SKM

SDs of ACF in SKM as primary carrier were prepared by solvent evaporation. An accurately weighed quantity of drug was transferred into mortar and dissolved in minimum volume of ethanol (95%) to produce a clear solution. Finally, SKM was added in appropriate proportion to the alcoholic solution of drug and mixed thoroughly until the solvent evaporated. The resultant SD was air-dried at 25°C and was scraped out as free-flowing dry powder. SDs were prepared in the ratios of 1:1, 1:3, and 1:5. SDs thus obtained were pulverized in a mortar and pestle and passed through sieve #80. Finally, the dried and pulverized product was preserved in desiccator for further use [23,24,37-40]. Composition of the formulations is provided in Table 1.

SDs in binary mixture of SKM-U

SDs of ACF in binary mixture of SKM-U were prepared as before in the ratios of 1:5:0.5, 1:5:0.75, and 1:5:1 [24,37-40]. Composition of the formulations is provided in Table 1.

SD in ternary mixture of SKM-U-CP

SDs of ACF in ternary mixture of SKM-U-CP were prepared as before in the ratios of 1:5:0.75:0.25, 1:5:0.75:0.50, 1:5:0.75:0.75, and 1:5:0.75:1 [25,26,37-40]. Composition of the formulations is provided in Table 1.

Drug-carrier compatibility study by Fourier-transform infrared spectroscopy

FT-IR spectroscopy study was carried out to assess the compatibility between ACF, SKM, urea, and CP. The pure drug (PD) and drug-SKM/SKM: U:CP physical mixtures were separately scanned in Bruker FT-IR spectrophotometer in the range of 4000–400 cm^{-1}. The pellets were prepared with potassium bromide on hydraulic press [3,27,41-44].

Physical appearance

SDs in SKM, SDs in binary mixture of SKM-U, and in ternary mixture of SKM-U-CP were visually inspected for color and texture [28,29,45-47].

Table 1: Compositions of solid dispersions of aceclofenac

Formulation code	ACF: SKM: U: CP
F1	1: 1: 0: 0
F2	1: 3: 0: 0
F3	1: 5: 0: 0
U1	1: 5: 0.5: 0
U2	1: 5: 0.75: 0
U3	1: 5: 1: 0
C1	1: 5: 0.75: 0.25
C2	1: 5: 0.75: 0.50
C3	1: 5: 0.75: 0.75
C4	1: 5: 0.75: 1

Yield

Percent yield of product was obtained by weighing the final formulation and comparing it with theoretical yield [30,31].

Determination of melting point

Capillary method was used to determine the melting points of PD, individual carrier components, as well as all the prepared formulations in digital melting point apparatus (Electronics India, Model-931) [25].

Drug content assay

SD containing about 10 mg of ACF was accurately weighed and transferred to a volumetric flask. About 450 ml of double-distilled water was added and flask was shaken to dissolve the formulation completely. Then, volume was made up to the mark with double-distilled water and the absorbance of this solution was measured at 270 nm against reagent blank. In each case, analysis was carried out in triplicate [23,24].

Determination of equilibrium solubility

Equilibrium solubility studies for pure ACF and SDs were carried out in double-distilled water and phosphate buffer (pH 6.8) at 25°C by shake-flask method. PD and SD (containing ACF equivalent to 6 mg) were added to Erlenmeyer flasks containing 50 ml of test medium. The dispersions were kept in gyratory shaker at 25°C for 24 h following which the samples were filtered through Whatman filter paper (No. 1), suitably diluted with corresponding medium and absorbances were measured spectrophotometrically at 270 and 273 nm respectively for double-distilled water and phosphate buffer (pH 6.8) [32,48-52]. Solubility of the formulations and corresponding % solubility enhancement with respect to the PD was calculated from the respective calibration curves using the following formula (Equation 1).

$$\%\ Solubility\ enhancement = \frac{Solubility\ of\ drug\ in\ formulation - Solubility\ of\ drug}{Solubility\ of\ pure\ drug} \times 100 \quad (1)$$

In vitro dissolution study

In vitro dissolution study for ACF and the prepared formulations was done in USP II dissolution rate test apparatus (paddle type) (Labindia D5 8000, Laboratory India) using 900 ml of phosphate buffer (pH 6.8) and double-distilled water at 37°C±0.5°C and 50 rpm. SDs equivalent to 6 mg PD were taken for the study. Aliquots of 4 ml were withdrawn at predetermined time intervals of 30 s till 4 min and at time intervals of 3 min until 30 min for study in phosphate buffer and double-distilled water, respectively, and replenished with fresh medium to maintain sink condition. The withdrawn samples were filtered, suitably diluted with the corresponding medium, and analyzed spectrophotometrically at 273 and 270 nm, respectively. Cumulative percentage of drug dissolved at each time point for each formulation in each medium was calculated from calibration curve and drug dissolution profiles were graphically plotted. For the data obtained in double-distilled water, t_{60} (time taken for 60% drug to dissolve) values were compared for better representation [36-38].

RESULTS AND DISCUSSION

Fourier-transform infrared spectroscopy

The IR spectrum of PD was compared with the spectra of ACF-carrier physical mixtures (Fig. 1). Peaks of PD were found to match with the reported ones [3,27]. No significant new peak appeared in SDs with binary or ternary carrier mixtures. No characteristic peaks of ACF could be seen in ACF: SKM:U: CP physical mixture which may be attributed either to masking of PD by the hydrotropic carrier mixture and also may be due to loss in crystallinity of the PD in SD. Thus, the carrier components and drug were found to be compatible with each other rendering SD formation viable.

Physical appearance

SDs of ACF in SKM, SKM-U, and SKM-U-CP were found to be off-white in color, free-flowing, and non-sticky in nature.

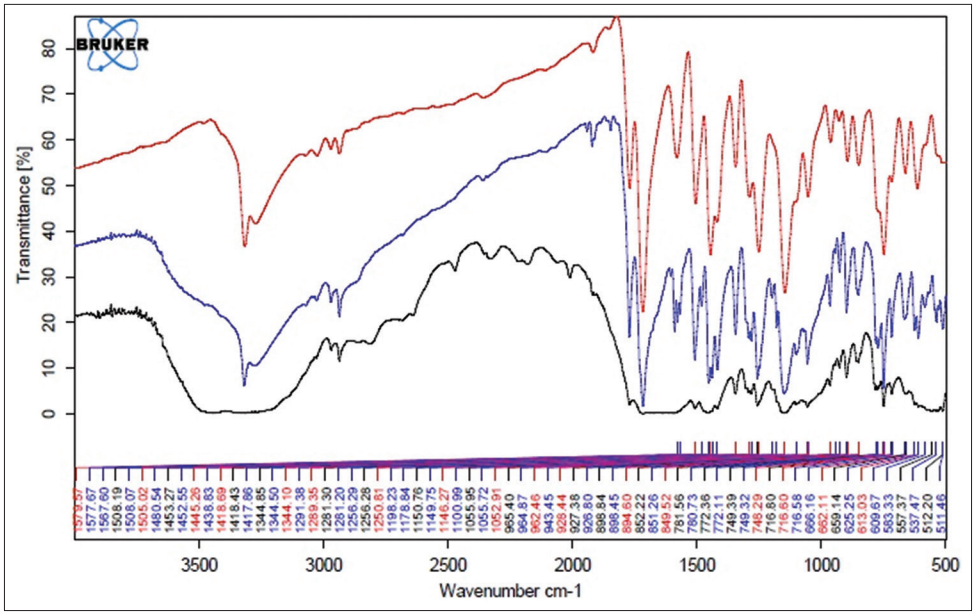

Fig. 1: Fourier-transform infrared spectra of ACF (RED), ACF: SKM (BLUE), ACF: SKM: U: CP (BLACK) physical mixtures

Yield

Yield of SDs was found to be in the range of 97–9% indicating suitability of the method in producing final product with minimum loss.

Melting point

The melting points of ACF, SKM, U, CP, and the formulations are given in Table 2. The melting points of the pure components were found to match with the reported values [25]. Formation of SDs in single, binary or ternary carrier mixtures resulted in shifting of the melting point of PD to lower side indicating probable reduction in crystallinity of the drug which may manifest itself as improved solubility in SDs. Among the various carrier components/mixtures studied, C2 produced maximum reduction in melting point of ACF, thereby possibly leading to SD with highest amorphicity, maximum % enhancement in solubility, and rapid drug dissolution.

Drug content

Drug content of the various formulations was found to vary between 98.6 and 99.2% indicating minimum loss in drug content during formulation development.

Solubility studies

Pure ACF was found to have solubility of 0.041 mg/ml and 0.080 mg/ml in double-distilled water and phosphate buffer (pH 6.8), respectively, at 25°C. Percent enhancement in solubility of SDs in both water and buffer has been graphically depicted in Fig. 2. The slope values for calibration curves of ACFw in double-distilled water and phosphate buffer were found to be 0.0175 and 0.0308, respectively, as obtained from Microsoft Excel, as shown in Figs. 3 and 4. Formulation C2containing ACF: SKM: U: CP in the ratio of 1: 5: 0.75: 0.50 demonstrated highest percentage of solubility enhancement of 83.92% and 49.69% in double-distilled water and phosphate buffer, respectively, compared to PD. Pure ACF showed higher solubility in buffer than in water and it is noteworthy that percentage solubility enhancement observed with SDs in buffer is approximately half of that in water. Thus, it can be concluded that with increase in the proportion of SKM, there was a consistent increase in solubility, with F3 exhibiting highest solubility enhancement in double-distilled water, and phosphate buffer than the PD. Addition of urea in small proportion as hydrotrope to SKM produced further improvement in solubility. The optimized formulation, U2, possessing ACF: SKM: U in the ratio of 1:5:0.75 demonstrated highest percentage of solubility enhancement of 75% and 36.51% in double-distilled water and phosphate buffer. Urea is reported to promote reduction in crystallinity

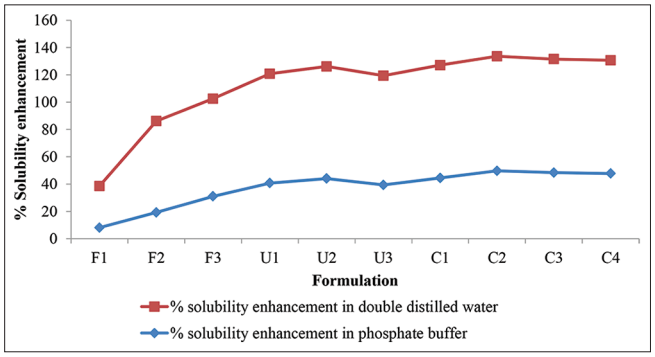

Fig. 2: Solubility enhancement (%) of different solid dispersions of ACF in double-distilled water and phosphate buffer (pH 6.8).

Table 2: Melting points of pure components and primary solid dispersions, solid dispersions in binary, and ternary carrier mixture

Formulation code	Observed values (°C)
ACF	159–165
SKM	17–25
U	136–138
CP	137–154
F1	152–154
F2	149–152
F3	148–150
U1	145–152
U2	146–151
U3	145–150
C1	139–147
C2	138–146
C3	143–145
C4	145–147

and to accumulate on hydrophobic surfaces of drug particles, thereby weakening interactions between hydrophobic particles [53-56]. Urea may have impacted entropy and shifted the dissolution equilibrium of ACF in buffer as well as water by interacting favorably with drug and SKM [57]. However, higher proportion of urea as in U3 failed to produce expected enhancement. With an aim to achieve still better solubility, superdisintegrant, CP was added in small parts to the binary carrier

Table 3: Parameters from dissolution profiles of pure drug and solid dispersions in phosphate buffer (pH 6.8) and double-distilled water

Formulation code	Phosphate buffer (pH 6.8)		Double-distilled water		
	Maximum cumulative percent release (CPR)	Time (sec) to achieve CPR	Maximum cumulative percent release (CPR)	Time (min) to achieve CPR	t60 (min)
PD	80.28	240	47.13	120	>120
F1	58.07	120	54.62	09	>9
F2	67.10	120	65.10	09	7.5
F3	68.03	90	82.37	09	4.17
U1	68.52	90	84.58	09	<3
U2	76.18	60	88.45	09	<3
U3	67.93	90	82.28	09	3.5
C1	78.02	60	90.00	09	<3
C2	85.67	60	98.55	09	<3
C3	79.85	60	92.45	09	<3
C4	79.38	60	91.45	09	<3

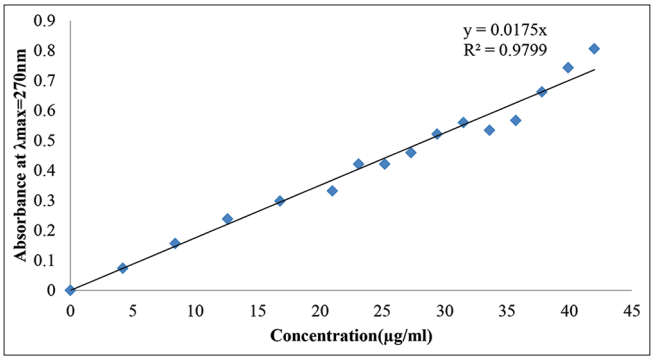

Fig. 3: Standard curve of ACF in double-distilled water

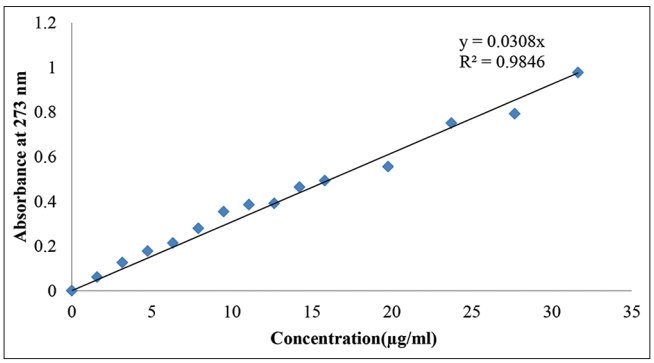

Fig. 4: Standard curve of ACF in phosphate buffer (pH 6.8)

mixture of SKM and urea. Several studies have reported the use of CP as single carrier component in formulation of SD [34-36,57]. Increase in level of CP beyond a threshold value did not produce any further improvement in solubility as observed with C3 and C4, with maximum enhancement being observed with C2 [33-35]. Improvement in solubility by addition of CP should also be reflected in drug dissolution profile.

***In vitro* drug release studies**

PD exhibited dissolution of only 47.13% in 2 h in water and 40.43% in 90 s in phosphate buffer. Formulation C2 demonstrated highest dissolution of 98.55% in 9 min and 85.67% in 60 s in water and phosphate buffer, respectively. When urea and CP were added sequentially as 2nd and 3rd components to the primary SD with SKM, t_{60} was found to be <3 min in water for all the formulations indicating significant increase in rate and extent of drug dissolution. On the basis of maximum percentage of drug dissolved, the prepared SDs can be ranked as (in both media).

C2>C3>C4>C1>U2 >U1> F3>U3 > F2>F1> PD and therefore, SD in ternary hydrotropic mixture produced not only significant improvement in drug dissolution profile in both aqueous medium and in buffer but also almost complete dissolution of drug when compared to PD alone or other SD formulations especially in water (Table 3). SD with SKM only increased solubility and improved dissolution profile, but >30% drug remained undissolved, even from the optimized formulation, F3. This observation necessitated incorporation of hydrotrope, urea and subsequently, superdisintegrant, and CP as carrier components. Addition of crospovidone as superdisintegrant to form hydrotropic SDs exerted marked positive influence on drug dissolution as predicted from solubility study, with more than 75% drug dissolved within 1 min in phosphate buffer. Binary carrier mixture of SKM-U failed to dissolve 80% drug within 90 s [58-62]. Therefore, CP facilitated rapid uptake of water by wicking phenomenon resulting in rapid drug dissolution, without forming any gel barrier [63,64]. However, increase in CP concentration above the threshold value produced no further improvement as maximum wetting and swelling of SD particles has been achieved in C2. Drug dissolution of CP-based formulations may not always follow linear relationship with CP concentration [65,66].

CONCLUSION

Therefore, it can be concluded that optimum ratio of drug: SKM: U: CP could produce significant improvement in solubility and dissolution rate of ACF in both water and buffer with expected beneficial effect on oral bioavailability. Thus, ternary mixture of SKM-U-CP as a combination of hydrophilic carrier-hydrotrope-superdisintegrant shows great promise in solubility enhancement and improvement in rate and extent of dissolution rate of poorly water-soluble drugs.

AUTHORS' CONTRIBUTIONS

The authors have contributed equally to content designing, writing, and editing of manuscript.

CONFLICTS OF INTEREST

No conflicts of interest by authors.

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