In Vitro Studies on Binary Mixture of Skimmed Milk and Urea as Solid Dispersion Carrier for Aceclofenac

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Abstract

Among the various strategies employed to enhance solubility, dissolution and bioavailability of poorly soluble drugs in vivo, formulation of solid dispersion using hydrophilic and/or water-soluble carriers with varying physicochemical characteristics seems to be a developable, economically viable and easy option. The present study is aimed to use skimmed milk(SKM)-urea(U) as a novel binary mixture of classical carrier-hydrotrope in solid dispersion of poorly water-soluble aceclofenac (ACF). Compatibility of ACF and binary mixture of SKM-U was confirmed by FTIR spectroscopic analysis. Solid dispersions of ACF-SKM and ACF-SKM-U were prepared in varying ratios of 1:1 to 1: 5 for ACF-SKM and 1:4.5:0.5, 1:4.25:0.75 and 1:4:1 for ACF-SKM-U by solvent evaporation technique using ethanol(95%) as the common solvent and were characterised by their physical appearance, solubility enhancement (compared to pure drug) in double distilled water and phosphate buffer (pH 6.8) at 25 ºC and drug dissolution profiles in the above mentioned media. Based on solubility enhancement data(71.53% and 31.03%) and maximum cumulative percentage release data (82.37% in 9 mins and 68.03% in 90 secs) in double distilled water and phosphate buffer respectively, ACF-SKM (1:5) was found to the best which was used for studying the effect of addition of urea as hydrotrope. ACF: SKM: U (1 : 4.5 : 0.75) exhibited maximum solubility enhancement of 75% .and 36.51% and cumulative percentage release of 83.83 % in 9 mins and 69.24% in 90 secs in double distilled water and buffer respectively. Therefore, the binary mixture of skimmed milk-urea has been proved to be marginally superior over skimmed milk in terms of solubility enhancement and drug release profile of aceclofenac.

Keywords : Binary mixture, carrier, hydrotrope, skimmed milk, solid dispersion, solubility enhancement, urea.

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1. Introduction

Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. The problems associated with the delivery of anactive agent via the oral route can be attributed to the fact that most of the drugs undergo poor absorption resulting the poor bioavailability [1-3]. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and intestinal fluids before it can travel across the membranes of the GI tract to reach systemic circulation. 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 gastrointestinal fluids [4-10].

Improvement in solubility can be acquired by the formation of solid dispersions with several hydrophilic or water-soluble substances or hydrotropes such as urea, lactose, mannitol, polyethylene glycols of MWs 4000, 6000, 8000, 10000, β-cyclodextrin, skimmed milk, HPMC, Poloxamer, sodium citrate, PVP-K30, sodium starch glycolate (SSG), crospovidone, croscarmellose sodium (CCS), para-amino benzoic acid (PABA)etc[7,9,11].

Solid dispersion refers to the group of solid products consisting of at least two different components, generally a hydrophilic carrier and poorly water-soluble drug where the carrier can be either crystalline or amorphous single substance or mixture of substances imparting desirable characteristics [12,13].Solid dispersion concept was first introduced by Sekiguchi and Obi in the early 1960s, who investigated the formation and dissolution performance of eutectic melts of a sulfonamide drug, griseofulvin and a water-soluble carrier, urea [14,15]. Solid dispersions hold great promise in increasing solubility, dissolution, absorption, bioavailability and hence, therapeutic efficacy of poorly water-soluble drugs in dosage form. In a solid dispersion, the drug is dispersed molecularly in solid state in solid carrier system. The mechanisms of enhancement of solubility and dissolution rate by employing solid dispersion 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].

Apart from enhancing bioavailability of poorly water soluble drugs through increased solubility/dissolution rate, solid dispersions also help in uniform distribution of small doses of drug in the solid state[16-20].Solid dispersions facilitate stabilization and protection of drugs vulnerable to decomposition by hydrolysis, oxidation, racemization, photo-oxidation etc.Masking of unsavory taste and odour and avoidance of undesirable incompatibilities are also possible.Liquid active pharmaceutical ingredients (APIs) may be converted into solid formulations for ease of handling and better shelf-life stability as observed with unsaturated fatty acids, essential oils, benzaldehyde, etc [3,21,22].

Aceclofenac is an orally effective Non-Steroidal Anti-Inflammatory Drug (NSAID) of phenyl acetic acid group. However, it is poorly water soluble, 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 to 103.17 µg/ml as obtained from various studies. In phosphate buffer (pH 6.8), solubility of 1058.9 to 1347.71 µg/mlhas been reported [3,5]. Its solubility characteristics shows that its bioavailability will be dissolution rate limited and it belongs to BCS (Biopharmaceutical Classification System) Class II. Thus, attempts should be made to improve its solubility and hence dissolution rate in aqueous medium and solid dispersion by use of binary mixture of skimmed milk(SKM) as carrier and urea as hydrotrope may show promise in improving oral bioavailability of aceclofenac.

Skimmed milk is readily available, cheap and easy to handle and thus has been employed as solid dispersion carrier for solubility, dissolution and bioavailability enhancement of poorly water-soluble drugs such as atorvastatin, simvastatin, loratidine where almost 20-30% solubility enhancement has been observed compared to pure drug and 2-3 fold increase in cumulative percent release has been obtained in aqueous

medium [3-7,11,13].Urea has been reported to produce significant improvement in the wettability, solubility and dissolution rate of drugs like olmesartanmedoxomil, clarithromycin, cefuroxime axetil[5,8].

The objective of the present study is to enhance the aqueous solubility and dissolution rateof aceclofenacby solid dispersion technique using binary mixture of skimmed milk-urea as a combination of carrier-hydrotrope. Till date, no study has employed binary mixture of hydrophilic carrier and hydrotrope as carrier for solid dispersion in enhancing solubility and hence bioavailability of poorly water-soluble drugs.

2. Materials and Methods

2.1 Materials

Aceclofenac was purchased from Yarrow Chem Products (Mumbai, Maharashtra), skimmed milk was purchased from Marvellous Overseas India Pvt Ltd (Indore, Madhya Pradesh) and urea(U) purchased from BA Chemie PvtLtd (Palghar, Maharashtra). All other reagents and chemicals utilized in this study were of analytical grade.

2.2 Methods

2.2.1 Preparation of solid dispersions (SDs)

Solid dispersions in skimmed milk

Solid dispersions of aceclofenac (ACF) in skimmed milk (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 ethanolic solution of drug and mixed thoroughly till the solvent evaporated. The resultant solid dispersion 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. Solid dispersions thus obtained were pulverized in a mortar and pestle and passed through sieve #80. Finally the dried and pulverised product was preserved in desiccator for further use[23,24]. Composition of the formulations is provided in Table 1.

Table 1. Compositions of solid dispersions of aceclofenac

Formulation Code	ACF : SKM : U
F1	1:1 : 0
F2	1:3 : 0
F3	1:5 : 0
U1	1:4.5:0.5
U2	1:4.25:0.75
U3	1:4:1

Solid dispersions in binary mixture of SKM-Urea(SKM –U)

Solid dispersions of aceclofenac in binary mixture of SKM-Urea were prepared as before in the ratios of 1:4.5:0.5, 1:4.25:0.75 and 1:4:1, by partial replacement of SKM in the optimised ratio and stored in desiccator[25,26]. Composition of the formulations is provided in Table 1.

2.2.2 Fourier transform infrared spectroscopy

FT-IR spectroscopy study was carried to assess the compatibility between aceclofenac, skimmed milk and urea. The pure drug and drug-SKM/SKM-U physical mixtures were separately scanned in Bruker FT-IR spectrophotometer in the range of 4000-400 cm^{-1}. The pellets were prepared on potassium bromide press[3,27].

2.2.3 Physical appearance

Solid dispersions in skimmed milk and solid dispersions in binary mixture of SKM –U were visually inspected for colour and texture [28,29].

2.2.4 Yield

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

2.2.5 Determination of melting point of pure materials

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

2.2.6 Preparation of standard curve of ACF

In phosphate buffer (pH 6.8)

A stock solution (1mg/ml) of ACF was prepared in phosphate buffer (pH 6.8). From the stock solution, a sub-stock (100µg/ml) was prepared. Solutions of varying concentrations in the range of 2 to 40 µg/ml were prepared from sub-stock solution. Absorbances of the resulting solutions were measured by UV-visible spectrophotometer (UV-1900I SHIMADZU) at $\lambda_{max}$of 273 nm against solvent blank. Absorbances were plotted against concentration to produce a calibration curve where R^2 and slope were calculated by MS-Excel.

In double distilled water

A stock solution (1mg/10ml) of ACF was prepared in double distilled water. Solutions of varying concentrations in the range of 10 to 100 µg/ml were prepared from stock solution. Absorbances of the resulting solutions were measured spectrophotometrically in UV-visible spectrophotometer (UV-1900I SHIMADZU) at λ_{max} of 270 nm against solvent blank. Absorbances were plotted against concentration to produce a calibration curve where R^2 and slope were calculated by MS-Excel.

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. Pure drug (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 ºC for 24 hrs following which the samples were filtered through Whatman filter paper(No. 1), suitably diluted withcorresponding medium and absorbances were measured spectrophotometrically at 270 and 273 nm respectively for double distilled water and phosphate buffer (pH 6.8) [32-35]. Solubilities of the formulations and corresponding % solubility enhancement with respect to the pure drug were calculated from the respective calibration curves by using the following formula(Equation 1).

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

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, Lab 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 pure drug were taken for the study. Aliquots of 1ml werewithdrawn at periodic time intervals of 30 secs till 4 mins and at time intervals of 3 mins till 30 minsfor study in phosphate buffer and double distilled water respectivelyand replenished with fresh medium to maintain sink condition. The withdrawn samples were filtered, suitably diluted with the corresponding medium and analysedby UV-visible spectrophotometer (UV-1900I SHIMADZU)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 buffer, t_{60} (time taken for 60% drug to dissolve) values were compared for better representation [36-38].

2.3 Results and Discussion

2.3.1 Fourier transform infrared spectroscopy

The IR spectra of pure drug were compared with the spectra of ACF-carrier physical mixtures (Figure 1). Peaks of pure drug were found to match with the reported ones[3,27].No significant new peak appeared or characteristic peak disappeared in physical mixture.Thus, the carrier components and drug were found to be compatible with each other rendering solid dispersion formation viable.

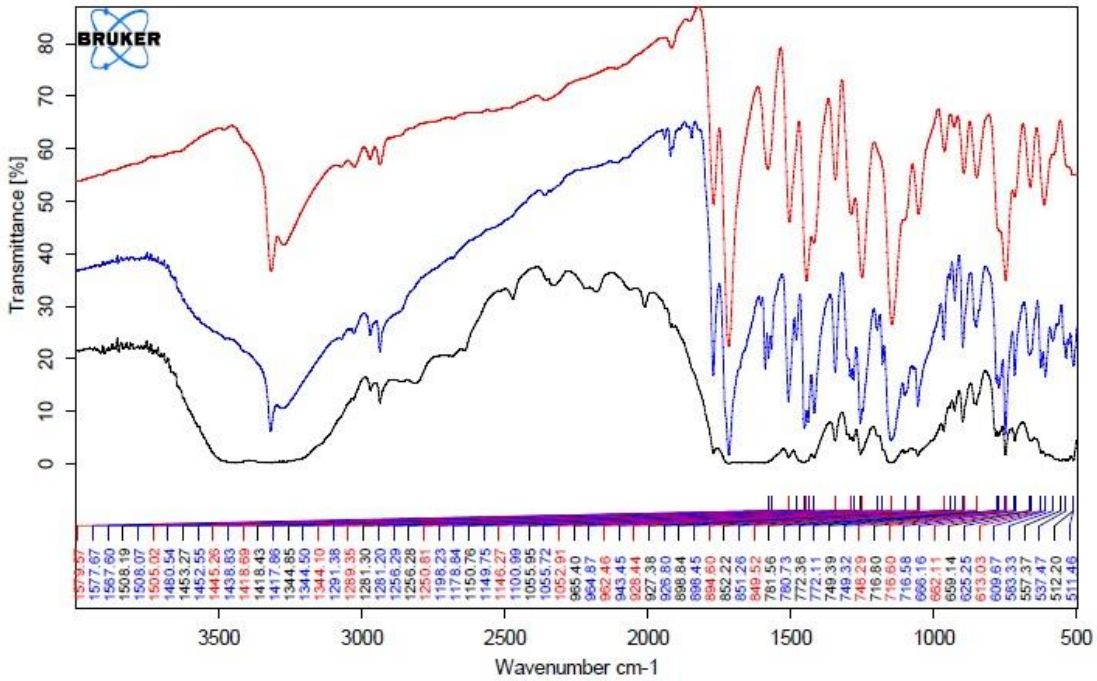

Figure 1: Fourier transform infrared spectra of ACF (red colour),ACF :SKM (blue colour), ACF : SKM : U (black colour) physical mixtures

2.3.2 Physical appearance

Solid dispersions of ACF in SKM and SKM-U were found to be off-white in colour, free-flowing and non-sticky in nature.

2.3.3 Yield

Yield of solid dispersions was found to be in the range of 97-99% indicating suitability of the method in producing final product with minimum loss (Table 2).

2.3.4 Melting point

The melting points of ACF, SKM, U, F1, F2, F3, U1, U2, and U3 are given in Table 2.The melting points of the pure components were found to match with the reported values [25]. Formation of solid dispersions resulted in shifting of the melting point of pure drug to lower side indicating probable reduction in crystallinity of the drug which may manifest itself as improved solubility in solid dispersions.

Table 2. Yield values and melting points of pure components and formulations

Formulation Code	Observed Values	Yield Values
ACF	159°C-165°C	-
SKM	17°C-25°C	-
U	136°C–138°C	-
F1	152°C–154°C	97.57 %
F2	149°C–152°C	98.80%
F3	148°C–150°C	98.95 %
U1	145°C–152°C	99.00 %
U2	146°C–151°C	98.50 %
U3	145°C–150°C	98.35 %

2.3.5 Standard curve of ACF

In phosphate buffer (pH 6.8)

Pure aceclofenac followed Beer-Lambert's law in the range of 0-32µg/ml in phosphate buffer (pH 6.8) shownin figure 2.

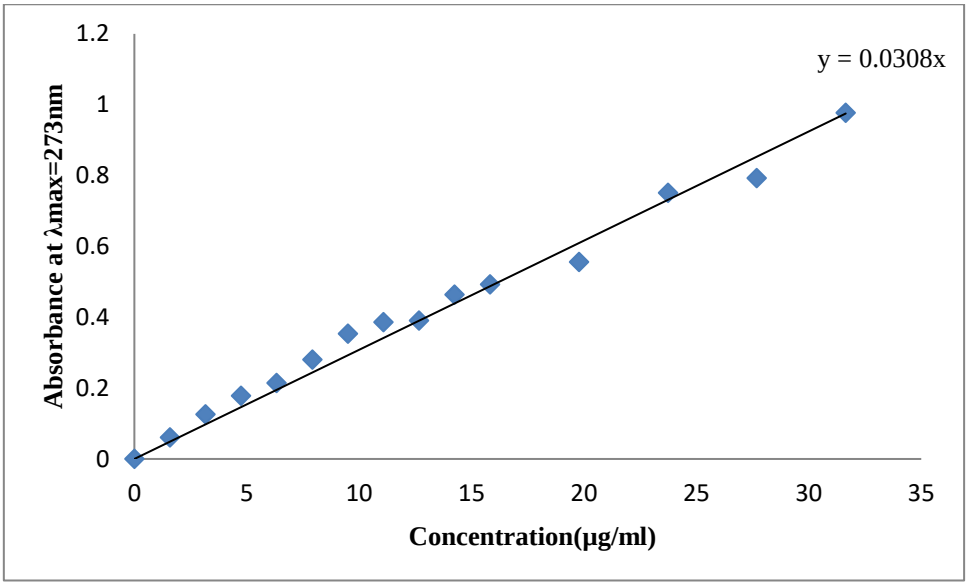

Figure 2:Standard curve of ACF in phosphate buffer (pH 6.8)

In double distilled water

Pure drug showed linearity in terms of concentration vs. absorbance in the range of 0-48µg/ml in double distilled water in figure 3.

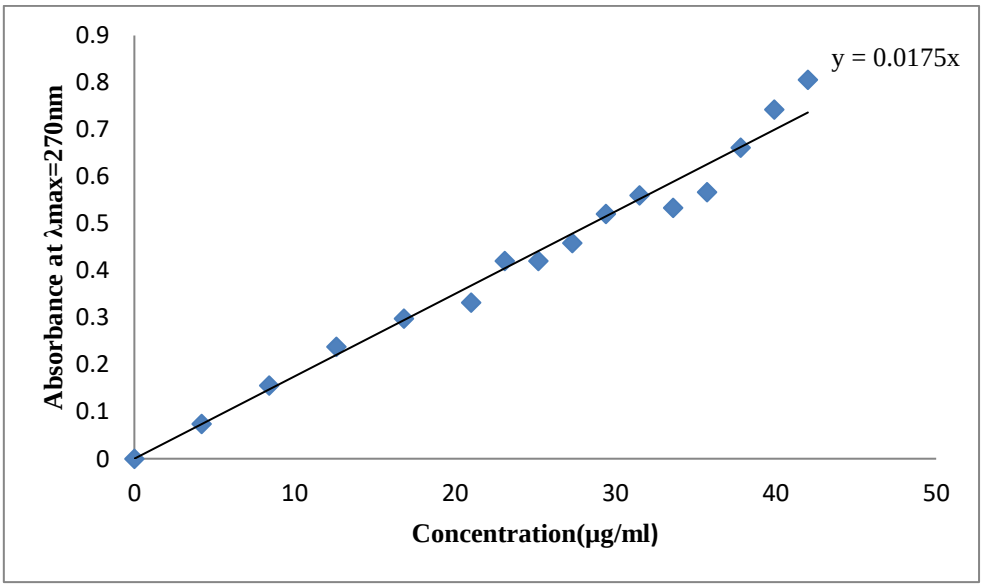

Figure 3: Standard curve of aceclofenac in double distilled water

2.3.6 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) at 25ºC. Percent enhancement in solubility of solid dispersionsin both water and buffer has been graphically depicted in figure 4. Formulation U2 containing ACF : SKM : U in the ratio of 1 : 4.25 : 0.75 demonstrated highest percentage of solubility enhancement of 75% and 36.51% in double distilled water and phosphate buffer respectively, compared to pure drug. Pure ACF shows 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. Addition of urea as hydrotrope to skimmed milk produced further improvement in solubility. But higher proportion of urea as in U3 failed to produce expected enhancement. Therefore, too much addition of urea to skimmed milk did not produce beneficial effect on drug's aqueous solubility [33-35].

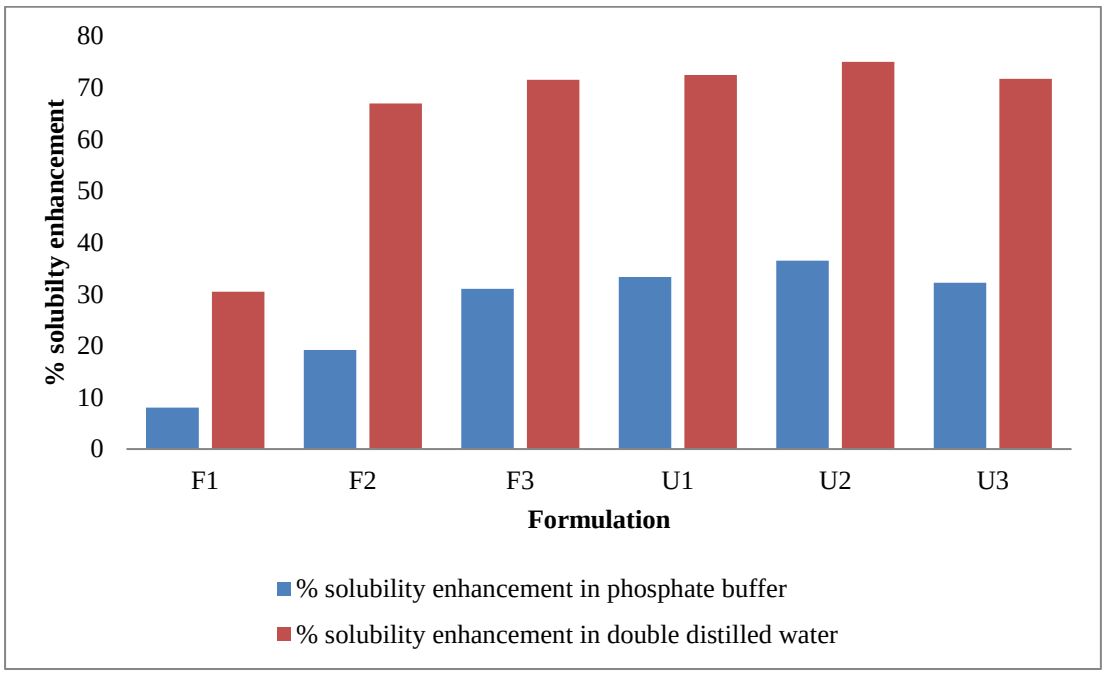

Figure 4: Solubility enhancement(%)of different solid dispersions of ACF in double distilled water and phosphate buffer(pH 6.8)

2.3.7 In vitro drug release studies

Pure drug exhibited dissolution of only 47.13%in 2 hrs in water and 40.43% in 90 secs in phosphate buffer.Formulation U2 demonstrated highest dissolution of 83.83%in 9 mins and 69.24%in 90 secs in water and phosphate buffer respectively.On the basis of maximum percentage of drug dissolved, the prepared solid dispersions can be ranked as

U2 > F3 >U1 >U3 > F2>F1> Pure drug in water and
U2 > F3 >U1 >F2 > U3>F1> Pure drug in phosphate buffer(pH 6.8).

Therefore, solid dispersion in binary mixture produced significant improvement in drug dissolution profile in both aqueous medium and in buffer (Table 3). Addition of urea as hydrotrope exerted positive influence on drug dissolution, except for U3 in buffer. Incorporation of urea in higher percentage did not produce additional benefit in terms of faster drug dissolution. For the simple solid dispersions of drug in SKM, higher ratios of carrier produced proportional improvement in rate and extent of drug dissolution[36,38].

Table 3.Parameters from dissolution profiles of pure drug and solid dispersions in phosphate buffer (pH6.8) anddouble 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	t_{60} (min)
ACF	80.28	240	47.13	120	>120
F1	57.5	120	53.53	09	>9
F2	67.1	120	60.98	09	7.5
F3	68.03	90	82.37	09	4
U1	60.23	90	72.8	09	4.83
U2	69.24	90	83.83	09	<3
U3	57.42	90	72.01	09	5

3. Conclusion

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

4. References

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