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Research Article

Preparation and evaluation of ciprofloxacin solid dispersion tablets developed from stearic acid, Polyethylene Glycol 4000 and Soluplus

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Abstract

Ciprofloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity used for the treatment of various bacterial infections and is characterized by poor aqueous solubility and low permeability. The aim of this study is to formulate and characterize ciprofloxacin solid dispersions using hydrophilic and lipophilic matrices for improved product qualities and drug delivery. Ciprofloxacin hydrochloride tablets were formulated as solid dispersions by melting and solvent evaporation in tablet moulds using varying concentrations of stearic acid (10-40 %w/w), Polyethylene glycol 4000 (PEG 4000) (10-40 %w/w) and Soluplus® (10-20 %w/w as ethanolic solution) as components. The prepared tablets were evaluated for weight uniformity, friability, hardness, Fourier transform-infrared spectroscopy (FT-IR), moisture uptake, swelling index, disintegration time and dissolution rate, using standard methods and optimization techniques. The results showed uniform solid dispersion weights with friability, hardness, moisture uptake and swelling index of 0.4-0.5%, 3.0-7.5 kgf, mostly <20% and 1-71%, respectively. The formulations were chemically stable with no transformational interactions between components. Formulations without stearic acid disintegrated within 30 min whereas those containing the lipid broke up after more than 1 h. Drug release studies showed high immediate release in tablets without stearic acid but with cumulative steady state release higher in formulations with 10 %w/w Soluplus and different concentrations of stearic acid and PEG 4000. In conclusion, ciprofloxacin was presented as solid dispersion tablets with modified physicochemical attributes for improved drug delivery.

Keywords: Ciprofloxacin; solid dispersion; drug delivery

INTRODUCTION

Some sensitive bacterial infections can be treated with ciprofloxacin, which is a fluoroquinolone antibiotic with a broad spectrum of activity. Ciprofloxacin act by inhibiting a type II topoisomerase (DNA gyrase) and topoisomerase IV [1], required to separate bacterial DNA, thereby inhibiting cell division during the reproductive process. Ciprofloxacin (hydrochloride) have a 'U' shaped pH-solubility profile with high solubility at pH values below 5 and above 10, and the profile usually show minimum solubility close to the neutral isoelectric point [2]. A low solubility of about 0.1-0.2 mg/mL is usually observed at around 6.8-7.5 pH conditions and 25-37 ºC. Extensive data on solubility, oral absorption, and permeability show ciprofloxacin to be in BCS Class IV based on Biopharmaceutics Classification System (BCS) [2].

Drug solubilization or dissolution is an essential rate-limiting step towards systemic absorption of drugs including ciprofloxacin. Various formulation approaches have been used to overcome the solubility and dissolution challenges of drugs [3,4]. These challenges can be successfully addressed by drug formulation as solid dispersions [5].

Solid dispersions are formulation techniques wherein one or more active pharmaceutical ingredient(s) are dispersed in inert carrier matrices at solid state usually prepared by the melting (fusion), solvent or melting-solvent methods [6]. In a state of solid solution, the drug can be in amorphous form, uniformly dispersed and effectively solubilized to improve bioavailability. Hydrophilic polymers, lipid matrices and solubilizers can be used to achieve some of these desired outcomes. Soluplus is a useful polymer for solid dispersions [7]. Furthermore, polyethylene glycols provide surface active and polymeric qualities which also improves the dispersion of the drug. Usually, an amorphous state develops which requires no energy to break the crystal lattice [8,9]. This blend of hydrophilic and lipophilic (hydrophobic) carriers is expected to allow improved solubilization by creating the right interfacial balance. In this research, Ciprofloxacin was formulated as solid dispersion tablets using stearic acid, polyethylene glycol 4000 and Soluplus as carriers and solubilizers for improved and controlled delivery of the drug.

MATERIALS AND METHODS

Materials

Stearic acid, PEG 4000 (Sigma Aldrich, USA), Soluplus (BASF, Germany). Ciprofloxacin hydrochloride was obtained as a gift directly from AC drug company (Enugu, Nigeria).

Formulation of ciprofloxacin solid dispersion tablets

A mixture of specified quantities of stearic acid and PEG 4000 (Table 1) was melted in a beaker using a water bath at 60 °C. Soluplus (50 mg, 100mg) was dissolved in 5 ml of ethanol. Ciprofloxacin (250 mg) and the ethanolic solution of Soluplus were added into the beaker containing stearic acid and PEG 4000 with continuous stirring. The molten mixture was transferred to empty tablet moulds and allowed to solidify as solvent evaporated and temperature reduced to ambient conditions (25 °C). The procedure was applied for all the batches (A-J).

Table 1: Quantities of ingredients required for ciprofloxacin solid dispersion tablets.

Ingredients	A	B	C	D	E	F	G	H	I	J
Ciprofloxacin (mg)	250	250	250	250	250	250	250	250	250	250
Stearic acid (mg)	75	100	50	150	-	100	133.3	66.7	200	-
PEG 4000 (mg)	75	50	100	-	150	100	66.7	133.3	-	200
Soluplus (alcoholic solution) (mg)	100	100	100	100	100	50	50	50	50	50
Total weight (mg)	500	500	500	500	500	500	500	500	500	500

Fourier transform infrared spectroscopy (FTIR)

The compatibility of the ingredients within the solid dispersion was evaluated by Fourier transform infrared spectroscopy. A 10 mg of each ingredient and pulverized tablet samples was analyzed using the FTIR instrument (Agilent Technologies, USA). Analysis of the powder samples was done over a scan range of 4000-650 cm^{-1} at % transmittance mode.

Measurement of weight uniformity of tablets

Twenty (20) moulded tablets were randomly selected from each batch of formulated ciprofloxacin tablets. Each solid dispersion tablet was weighed individually using an electronic balance (Mettler Toledo B204-S, Germany). The mean, standard deviation and percentage deviation were determined to assess the quality of the batches.

Measurement of hardness (crushing strength)

Ten tablets were randomly selected from each batch and individual hardness measured using Monsanto Hardness Tester (Monsanto, USA). The mean hardness value (KgF) and standard deviation of ten tablets of each formulation batch was obtained. The assessment was done by applying force on the tablets diametrically.

Evaluation of tablet friability

Ten moulded tablets were randomly selected for this study. The ten tablets were de-dusted and accurately weighed together using an electronic balance and the initial weight was recorded. They were then placed in a friabilator (Erweka, Germany) set to rotate at 25 rpm for four (4) minutes. After rotation, the tablets were removed, dedusted and the final weight was determined. The percentage friability of the tablet batches was calculated using Equation 1

$$Percent\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \ldots 1$$

Determination of Swelling Index

One tablet of a known weight from each formulation batch was placed into a petri dish containing 20 mL of 0.1 N HCL. At each designated time interval, the tablet was withdrawn, and excess fluid removed with non-adherent paper, then re-weighed. After the intervals (10, 20, 30, 60, 90 and 120 min), weights of tablets were measured for a period of 2 h. Percentage weight gains of the tablets were calculated and swelling index was obtained using Equation 2

$$Percentage\ swelling\ index\ (S.I) = \frac{W_t - W_0}{W_0} \ldots 2$$

W_t = weight of tablet at time t (min),

W_0 = weight of tablet at zero time

Moisture uptake studies

One tablet from each formulation (A-J) was weighed (W_0) and placed in the upper chamber of a desiccator at a relative humidity of 84% containing saturated potassium chloride solution in the lower chamber. After each day, each tablet was withdrawn and weighed for a period of five (5) days. Percentage moisture uptake of the tablets was calculated using Equation 3

$$Percentage\ moisture\ uptake = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100 \ldots 3$$

Disintegration time

Six (6) tablets were randomly selected from each of formulations A-J. A solution of 0.1 N HCL was used as disintegration medium. One tablet was placed in each of the six tubes in disintegration apparatus (Erweka, Germany), immersed in 500 ml 0.1 N HCl at 37 °C and the time taken for each tablet to completely breakdown to particles and pass through the wire mesh was determined. Basic statistical analysis was done to establish mean disintegration time and standard deviation.

Dissolution rate studies

The dissolution rates of ciprofloxacin from the moulded tablets were studied in a dissolution apparatus (Veego, Mumbai, India) using the USP paddle method. Briefly, each randomly selected tablet was immersed in 900 ml of 0.1 N HCl in the apparatus maintained at 37 ±1 ºC and stirred at 50 rpm. Series of 5 ml volumes of test solutions were withdrawn at different time intervals for 24 h and filtered. Each withdrawn sample was replaced with an equal volume of the medium

maintained at 37 ±1 ºC. The test samples were assayed by measurement of their absorbances at 272 nm using the UV spectrophotometer (Jenway 7305, UK).

Optimization using a simple 2^2 factorial design

A simple optimization study was done using 2^2 factorial design to establish main effects and interaction effects of two independent variables each with two levels. The selected independent variables are amounts of stearic acid (A) and PEG 4000 (B), both used at low level (50 mg) and high level (100 mg). The low and high levels of the independent variables were coded as -1 and +1 respectively, and the dependent variable (response) evaluated are crushing strength (CS) and friability since these target physical attributes are usually difficult to achieve without prior design in mould-based solid dispersions.

The data was analyzed using Design expert® 13 to generate predictive equations and plots (response surface) which establishes the design space.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum is presented in Fig. 1. It shows the spectrum of ciprofloxacin with NH- stretch observed at 3526 cm^{-1} which signifies presence of primary amines. A carbonyl stretch was also observed around 1699.7 cm^{-1}. In the stearic acid spectrum, -CH_2 stretch was observed around 2914.8 cm^{-1} while these peaks were observed at 2881 cm^{-1} for PEG 4000. Soluplus spectrum showed a broad band at 3432.9 cm^{-1} signifying presence of -OH and a peak observed at 2888.7 cm^{-1} represents -CH_2 stretching. The spectrum of the formulation showed these peaks although there were few points of slight differences due to proximity of peaks from different functional groups.

Weight Uniformity

The percent weight deviations from the mean weight of the solid dispersion tablets (Table 2) were less than 5%, which indicated batch acceptability. Weight uniformity provides an assumption of the amounts of ciprofloxacin in the tablets however, it is not a guarantee that the API is uniform in all tablets especially in formulations with low dose drugs. Furthermore, the observed weight uniformity of the tablets increases the probability of achieving intra-batch uniformity in disintegration times and dissolution rates.

Hardness (crushing strength)

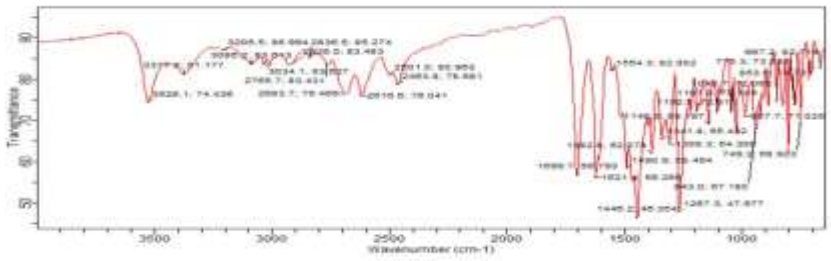
The crushing strength of the tablets are presented in Table 2, and it shows acceptable values within 4.30-6.95 KgF. The highest crushing strength (6.95 Kgf) was observed in batch D with 150 mg (30 %w/w) of stearic acid and 100 mg (20 %w/w) of Soluplus. The high presence of a solid lipid (stearic acid) with melting point of around 69 °C and Soluplus (a graft polymer) in this batch could have significantly increased the crushing strength of the tablets. Conversely, formulations (F) with 100 mg (20 %w/w) stearic acid in combination with 100 mg (20 %w/w) PEG 4000 and 50 mg (10 %w/w) of Soluplus resulted in relatively weakest solid dispersion tablets with 4.30 Kgf crushing strength.

The results show that delicate balance of lipid, polyethylene glycol and Soluplus is required to achieve any desired crushing strength.

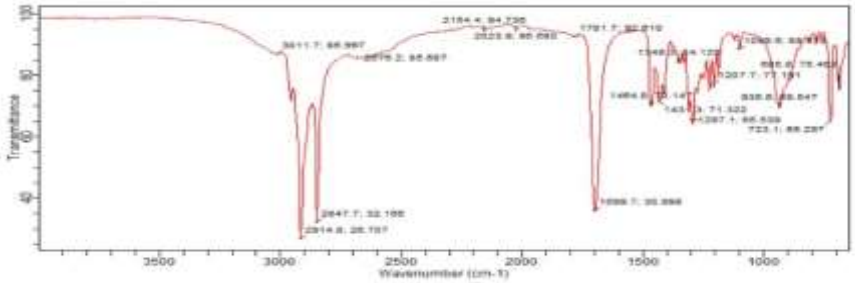
After optimization studies based on simple 2^2 factorial design (Table 3), the equation that best predict the outcome and describes the design space is presented as Equation 4:

$$CS = 5.00 - 0.475A - 0.300B + 0.075AB \ldots\ldots\ldots\ldots .4$$

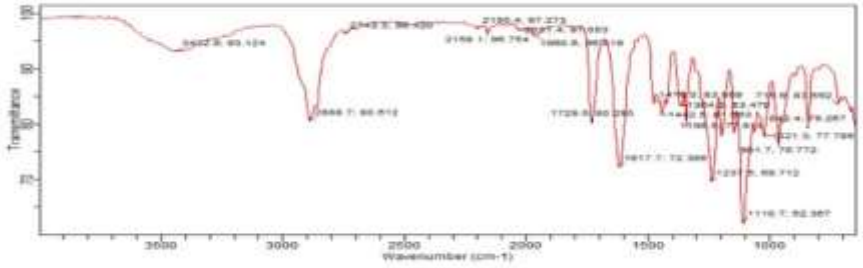
The main effects of stearic acid and PEG 4000 on the crushing strength are reductive as shown by the corresponding negative values although the negative or positive manifestations will depend on whether a low or high concentration is used. However, using the two excipients together increases the crushing strength slightly. Furthermore, fig. 2 show the 3D response surface and contour plots which expresses the design space and points where desired attributes can be selected. The application of these derivations is limited by the constraints of the chosen lower and upper limits of the independent variables.



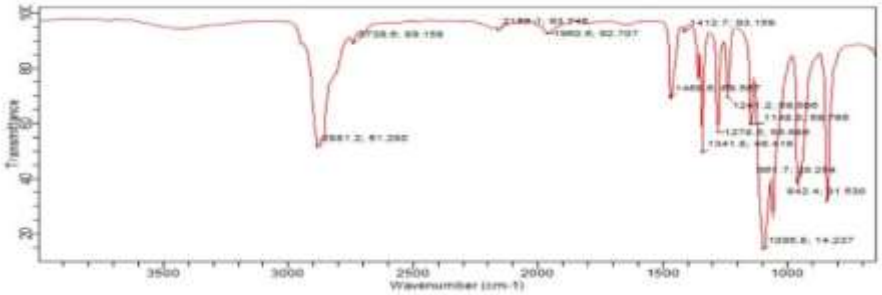
a (ciprofloxacin)



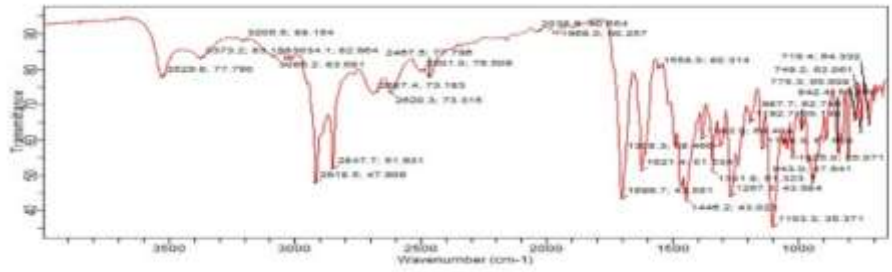
b (stearic acid)



c (Soluplus)

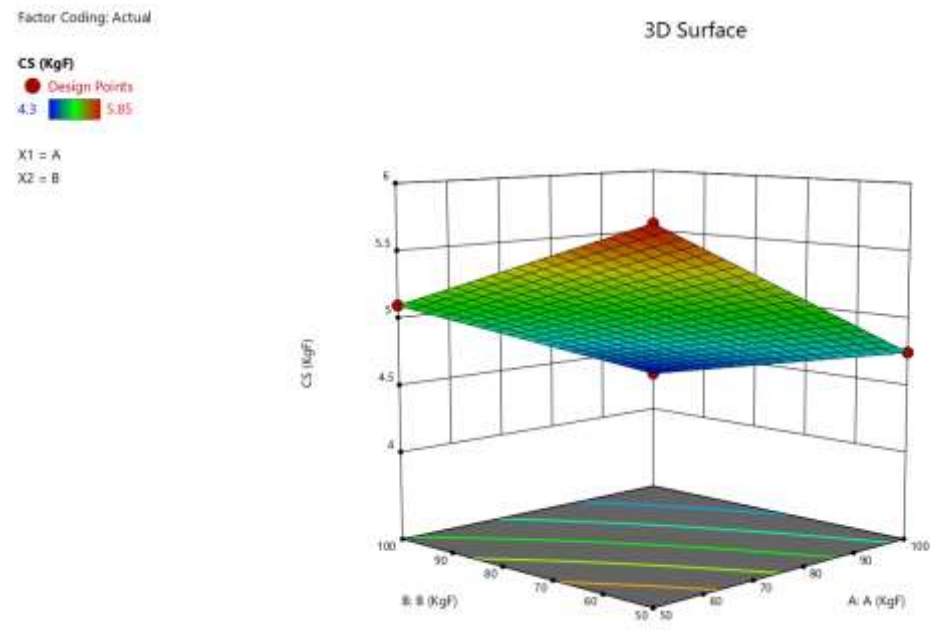


d (PEG 4000)

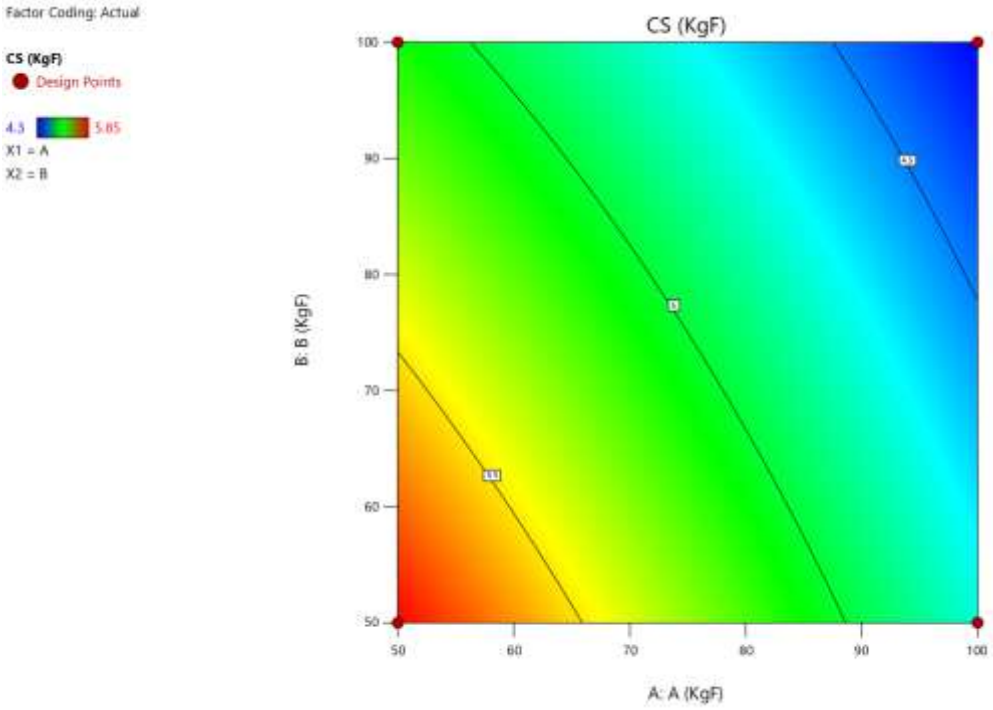


e (formulation)

Figure 1: FTIR spectra of (a) ciprofloxacin (b) stearic acid (c) Soluplus (d) PEG 4000 (e) formulation



a



b

Figure 2: 3D response surface (a) and response surface contour plots (b) for crushing strength

Tablet friability

The friability values (Table 2) of the tablets were all less than 1% which implies the tablets' resistance to attrition were all within acceptable limits. Ciprofloxacin (250 mg, 50 %w/w) formulations containing 50 mg (10 %w/w) stearic acid, 100 mg (20 %w/w) PEG 4000 and 100 mg (20 %w/w) Soluplus had the highest friability with 0.92%. The presence of 10 %w/w stearic acid which presents a diluted lipid content in combination with PEG 4000 and Soluplus caused weak zones within the solid matrices, resulting in higher friability.

Interestingly, some formulations did not show any breakaway particle after rotation at 25 rpm for 4 min. This tablet quality shows that losses of tablet parts due to transportation or bulk motion will be minimal.

After analysis, the following Equation 5 describes the design space:

$$Friability = 0.405 - 0.115A + 0.105B - 0.295AB \ldots\ldots\ldots 5$$

Within the selected design space, Equation 5 and fig. 3 show that combining stearic acid and PEG 4000 is expected to reduce the friability of the tablets.

Swelling index

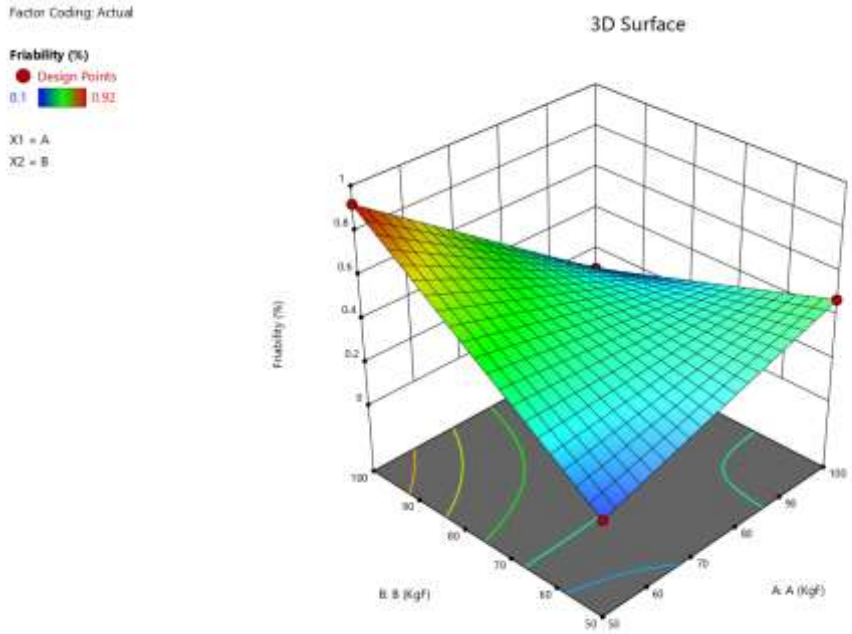
The swelling indices (Table 2) of batches B, A, C, recorded as 70.8, 63.6 and 58.7 % respectively, were observed to be significantly higher than values obtained for other formulations. The tablets with higher swelling were prepared with relatively lower quantities of stearic acid and PEG 4000 but with higher concentrations of Soluplus. The higher quantities of Soluplus in these tablets increased its swelling

since Soluplus is soluble in water and will allow passage of water through solid solutions prepared with it (Soluplus). Soluplus also comprises polyethylene glycol moieties in its structure. Furthermore, lower lipid content of these formulations reduced the lipid interference to aqueous-based swelling. The swelling process also serve as a rate limiting step to disintegration and eventual dissolution.

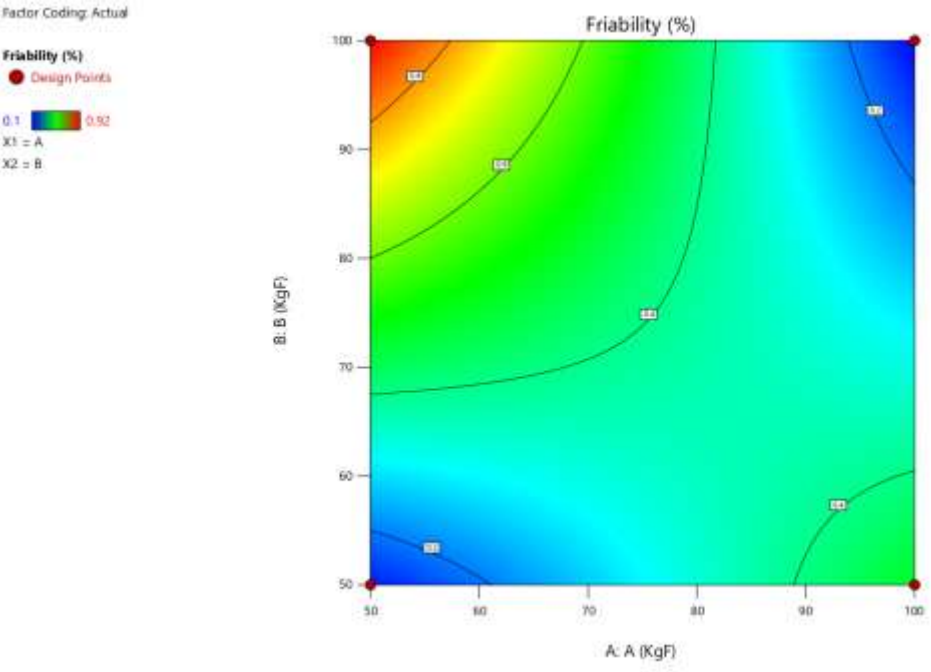
Moisture uptake

The moisture uptake of the tablets was less than or equivalent to 42 % (Table 2). Although most of the preparations with high moisture uptake were formulated with higher PEG concentrations relative to stearic acid, however, the highest value was observed in those with a 1:1 combination of the two excipients, showing an interplay or combination of factors.

Polyethylene glycol (PEG) is a hygroscopic polymer that undergoes deliquescence when a critical relative humidity condition is present [10]. This attribute is a factor for the increased moisture uptake observed in formulations containing relatively high PEG 4000. However, the presence of stearic acid and Soluplus implies that the overall influences on moisture uptake would depend on combination of factors.



a



b

Figure 3: 3D response surface (a) and response surface contour plots (b) for percentage friability

Disintegration time

The ciprofloxacin solid dispersions disintegrated within 22.3-285 min as presented in Table 2. The disintegration times of tablets without stearic acid (wax) (Batches J and E) were 22.3 and 24.5 min respectively, which were significantly lower ($p<0.05$) than others. This is expected since excess lipid matrices will reduce the ability of water to percolate the matrices of the solid dispersion tablets, a percolation process that facilitates disintegration of the tablets. Extended disintegration times of up to 285 min and 273 min were observed in formulations (D and I) with high concentrations of stearic acid and without PEG 4000. This prolonged disintegration process is expected to delay the release of ciprofloxacin from the solid dispersion matrices since disintegration is a rate limiting step for dissolution.

Drug release profile

The release profile of ciprofloxacin solid dispersion tablets is presented in fig. 4.

Formulations H and E containing relatively higher PEG 4000 concentrations released the ciprofloxacin faster with about 72% released after 1 h for batch H and 62% after 2 h for batch E. A sustained release, steady state situation was maintained afterwards. Formulation D, which has no PEG 4000 but contain high stearic acid content, had the lowest percentage drug release and this may also be related to having the longest disintegration time.

It is considered effective to apply polymers and other components to create matrices containing both hydrophobic and hydrophilic substituent groups, where the hydrophobic group facilitate interaction with the drug in an aqueous environment and inhibit crystallization, while the hydrophilic groups improve interactions with water and increase drug release from the system [11,12].

As the tablet swells because of water penetration through hydrophilic channels created by hydrophilic components in Soluplus and PEG 4000, the ciprofloxacin may be solubilized in tiny 'mixed component' droplets that allow for dissolution in the aqueous environment. Furthermore, the hydrophilic nature of these polymers enhances drug dissolution by increasing formulation wettability [13].

Table 2: Critical quality attributes of ciprofloxacin solid dispersion tablets

Formulation	A	B	C	D	E	F	G	H	I	J
Mean Weight (mg)	499.5	493.0	496.0	496.5	500.0	497.5	501.5	501.5	507.0	505.0
Crushing strength (KgF)	5.15	4.75	5.10	6.95	4.40	4.30	5.55	5.40	4.60	5.60
Friability (%)	0.41	0.48	0.92	0.39	0.46	0.00	0.00	0.00	0.43	0.00
Swelling index (%)	63.6	70.8	58.7	38.5	13.0	40.4	3.9	7.8	8.5	5.8
Moisture uptake (%)	41.9	4.3	4.0	4.2	18.2	4.3	6.1	25.5	8.2	11.8
Average Disintegration Time (min)	65.5	271.2	102.5	285	24.5	113.8	100.8	116.3	272.8	22.3

Table 3: Factorial design data for crushing strength and friability

Code	Stearic acid (mg)	PEG 4000 (mg)	Crushing Strength (KgF)	Friability (%)
-1, -1	50	50	5.85	0.12
-1, +1	50	100	5.10	0.92
+1, -1	100	50	4.75	0.48
+1, +1	100	100	4.30	0.1

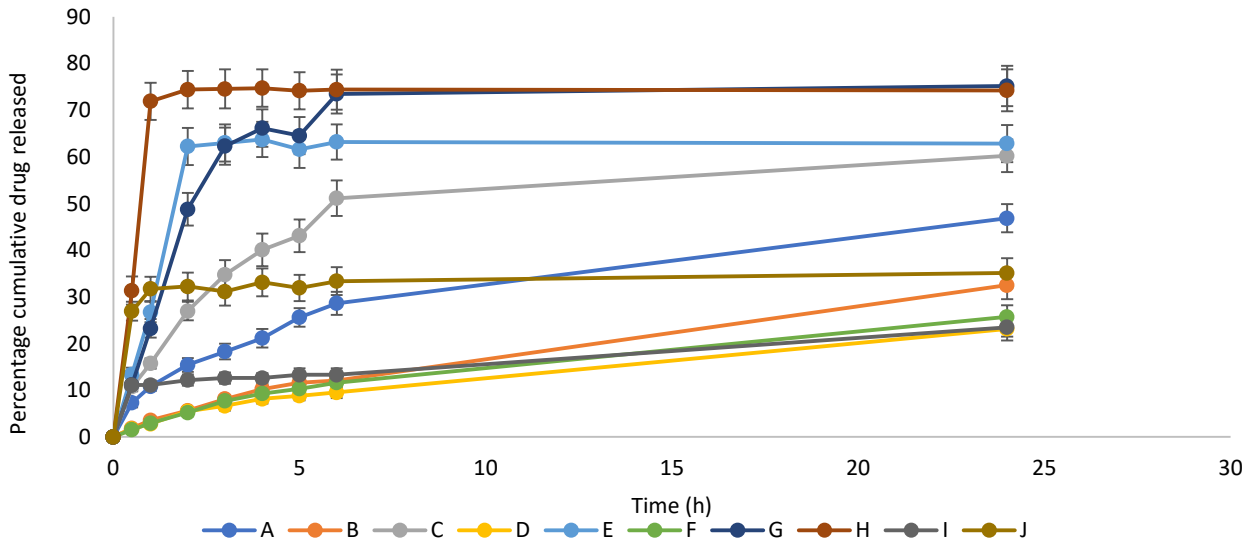


Figure 4: Ciprofloxacin release from solid dispersions based on stearic acid, PEG 4000 and Soluplus

CONCLUSION

Ciprofloxacin was presented as solid dispersion tablets, with the drug entrapped in matrices of PEG 4000, Soluplus and stearic acid to provide polymeric, solubilizing and lipid characteristics to the system.

The crushing strength and friability of the mould-based solid dispersion tablets were optimized for improved physical qualities. Moisture uptake and swelling index showed the composition-dependent dynamic behaviour of the delivery system in the presence of water and the values obtained will allow proper formulation and storage for stability and integrity of the tablets. Short and long disintegration times can be designed for the tablets and drug release can be relatively fast or sustained depending on the application. Ciprofloxacin solid dispersions were presented as tablets based on hydrophilic and lipid components for improved physical and functional qualities.

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