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Original Article

Enhancement of Dissolution rate of Ciprofloxacin by using various Solid Dispersion Techniques

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ABSTRACT

The aim of this research wok is to formulate and evaluate Ciprofloxacin solid dispersions system by using the different techniques. This will increase the solubility of the drug or Ciprofloxacin and give the immediate release of the drug from the formulations. The main objective is to formulate a drug product as immediate release oral solid dosage form of Ciprofloxacin solid dispersion system which is considered to be stable, robust quality and enhanced dissolution rate. To optimize the method of manufacture by formulate the Ciprofloxacin solid dispersion system by various techniques like Physical mixing, Co-grinding, Kneading and solvent evaporation techniques. The disintegrating agent used in the present study is Croscarmellose sodium.. To study the dissolution of Ciprofloxacin solid dispersion system by using the Physical mixing, Co-grinding, Kneading and solvent evaporation techniques, Optimization of formula. Among the four different techniques used for preparation o solid dispersions solvent evaporation technique has shown the increase in dissolution rate that is the Trail-5 was found to have a faster solubility and dissolution property which was prepared by using Croscarmellose sodium as a disintegrant in the ratio of 1:1.

1. INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause in sufficient bioavailability rather

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than the limited permeation through the epithelia and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges tom formulation scientists in the industries [1]. The term solubility is defined as maximum amount of solute that can be dissolved in a given amount of Solvent quantitatively it is defined as the concentration of the solute in saturated solution at a certain temperature in qualitative terms, solubility may be defined as spontaneous interaction of two or more substances to form a homogenous molecular dispersion [2].

Mechanism of action

Ciprofloxacin is a semi-synthetic (partially man-made), oral antibiotic in the cephalosporin family of antibiotics that stops bacteria from multiplying by preventing bacteria from forming the walls that surround them and it inhibit the cell wall synthesis. The walls are necessary to protect bacteria from their environment and to keep the contents of the bacterial cell together; bacteria cannot survive without a cell wall [3].

Solid dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [4] .Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 2. Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed [5]. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions [6].

Advantages of solid dispersion

Particles with reduced particle size, Particles with improved wettability, Particles with higher porosity, Drugs in amorphous state [7].

Preparation methods of solid dispersions [8]

(a) Solid dispersion techniques.

(b) Solvent evaporation method.

(c) Fusion method/melting method.

(d) Hot melt extrusion.

(e) Supercritical fluid technology (SCF).

(f) Dropping method.

(g) Electrostatic Spinning Method.

(h) Co-precipitation method.

2. MATERIALS AND METHODS

2.1 Materials

Ciprofloxacin (Pellets Pharma Ltd), Croscarmellose Sodium (Diocon Pharma Ltd), Distilled Water, Methanol, Di - Chloro methane, Potassium Di-hydrogen Phosphate, Sodium Hydroxide.

Instruments used

Digital Balance – Semsung AN ISO 9001-2004, Tray Dryer – ELITE scientific, Dissolution apparatus – VEEGO, U-V spectrophotometer – Spectro 2080 plus Analytical technologies limited, Distillation Tank – JSGW double distillation plant.

2.2 Experimental methods

2.2.1 Estimation of Ciprofloxacin

A Simple Sensitive and accurate Spectrophotometric method was used for the measurement of Ciprofloxacin at a λ max 288nm.The absorbance of standard dilutions were measured at 288nm.

procedure

The standard solutions of Ciprofloxacin were subsequently diluted with pH 7.2 Phosphate buffer to obtain series of dilutions containing 5,10,15,20, and 30 µg of Ciprofloxacin solution [9]. The absorbances of above dilutions were measured in Spectro 2080 plus Analytical technologies limited U-V Spectrophotometer at 288 nm using distilled water as

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blank. The concentration and the corresponding absorbance values were given in Table 5. The absorbance values were plotted against concentration of Ciprofloxacin as shown in Figure -2.

2.2.2 Drug release studies

Dissolution studies on each formulation were performed in a calibrated eight station dissolution test apparatus equipped with paddles employing pH 7.2 phosphate buffers as medium. The paddles were operated to rotate at 75 rpm and the temperature was maintained at 37± 1^0c throughout the experiment. Samples were withdrawn at regular intervals up to 60 min and replaced with equal volume to maintain the constant volume of dissolution medium throughout the experiment [10]. Drug content of the samples was determined by Spectro 2080 plus Analytical technologies ltd UV Spectrophotometer at 288nm after suitable dilution of samples [11]. Necessary corrections were made for the loss of drug due to each sampling. The drug dissolved experiments were conducted in triplicate. The dissolution profile were depicted in Table-12 to 13 and shown in Fig-13. The zero order and first order plots and their corresponding release constant were given in Table – 6 to 10 and shown in Figure-3 to 12.

Dissolution Test Acceptance Criteria

Acceptance criteria for dissolution tests are set on the basis of requirements for a percent quantity of drug to be released after a certain period of time in the dissolution apparatus. Since each test is usually conducted using six individual dosage units, acceptance criteria must be established on this basis. The compendia recognize that reasonable tolerances are required to ensure that criteria are not prohibitive, but at the same time, they need to discriminate between acceptable and unsatisfactory batches of products. The approach developed within various compendia is now harmonized for immediate release and extended release—though not for delayed release—and allows for three levels of staged testing. For immediate release products, acceptance criteria are based on a single time point and a single value, expressed as a Q value [11]. Then, at each of the three stages, the specification requires that mean values not be less than Q, but a set number of individual units are allowed to release a percent quantity of active which may be as low as Q - 25% for one unit at stage three [12].

For extended release products, specifications are based on three or four time points. For the intermediate time points, the requirements are based on ranges; for the final time point, they are usually based on a single value. Therefore, the acceptance criteria at each stage are expressed in terms of variances around ranges for intermediate time points and minimum acceptable release at the final time point [13].

2.2.3 Determination of amount of drug content

The amount of drug substance present in the given dissolution samples were determined with the help of UV-Spectrophotometer at a wavelength of 288nm. The obtained absorbance values were substituted in the given equation to get the amount of drug substance at different time intervals of dissolution.

$$\text{Amount} = \frac{\text{Test o.d}}{\text{Standard o.d}} \times \text{dilution factor} \times 900 / 1000$$

2.2.4 Procedure for Assay

The amounts of drug present in the taken oven formulations were determined with the help of U-V Spectrophotometric method. For each batch 100 mg of sample was taken in to the volumetric flask and add methanol and the mixer was diluted with the pH 7.2 phosphate buffer. The dilutions are made as 5, 10, 15, 20 and 25 µg/ml. The absorbance of solution was determined at 288 nm by U-V Spectrophotometer. The

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resultant drug content and practical yield was shown in the Table 11.

2.2.5 Different formulation batches

Formulation 1 - PURE DRUG (100mg)

Formulation 2 – DRUG: POLYMER (1:1) Croscarmelose sodium

Physical Mixing

Accurately weighed required amount of Ciprofloxacin and Croscarmelose Sodium (carrier) in 1:1 drug-to-carrier weight ratio were mixing thoroughly in a mortar until a homogeneous mixture was obtained for 3 min. The product was kept in desiccators at room temperature until for further study or investigation

Co-grinding Technique

Required quantity of drug was accurately weighed and transferred in to mortar to this adds requires quantity of Croscarmelose sodium in the ration of 1:1 were mixing thoroughly until a homogenous mixer was obtained. Triturating was carried in 10 -15 min to form a homogenous mixer. The product is packed and kept in a dedicator at room temperature until for further study or investigation.

Formulation3-

DRUG:POLYMER(1:1)Croscarmelosesodium

Kneading method

Drug and polymer was mixed with the small amount of the solvent i.e. water to form a thick paste by kneading and hence it was dried at 45ºC in a tray dryer. The mass was passed through the sieve no. 30 and stored in the desiccators. The product is packed and kept in a dedicator at room temperature until for further study or investigation.

Formulation 5– DRUG: POLYMER (1:1) Croscarmelose sodium

Solvent evaporation method

Required amount of drug is accurately weighed and transfer in to mortar. The drug and the polymer were dissolved in sufficient volume of dichloromethane with continuous stirring. The solvent was then completely evaporated at room temperature with continuous stirring to obtain dry granules. The resulting solid dispersion was stored in airtight container till further use.

Table 1: Formulation 2 (physical mixing).

S.NO	INGREDIENTS	QUANTITY
1	Ciprofloxacin	100mg
2	Croscarmelose sodium	100mg

Table 2: Formulation 3 (Co-grinding technique)

S.NO	INGREDIENTS	QUANTITY
1	Ciprofloxacin	100mg
2	Croscarmelose sodium	100mg

Table 3: Formulation 4 (kneading method)

S.NO	INGREDIENTS	**QUANTITY**
1	Ciprofloxacin	100mg
2	Croscarmelose sodium	100mg
3	Distilled Water	Quantity sufficient

Table 4: Formulation 5 (solvent evaporation method)

S.NO	INGREDIENTS	QUANTITY
1	Ciprofloxacin	100mg
2	Croscarmelose sodium	100mg
3	Dichloromethane	Quantity sufficient

3. RESULTS AND DISCUSSION

Trial-1

This trail was done by using pure drug; it has shown poor dissolution property because of less solubility of drug in the dissolution medium.

Table 6: Kinetic profile of Ciprofloxacin F-1(Pure drug)

S.NO	Time	OD	Amount of drug dissolved	%Drug dissolved	%Drug remained	Log% Drug remained
1	0	0	0	0	100	2
2	5	0.195	83.97	84.78	15.22	1.182
3	10	0.203	81.41	88.25	11.75	1.07
4	15	0.213	91.72	83.34	16.66	1.221
5	20	0.227	97.75	98.69	1.31	0.117

Table 7: kinetic profile of ciproploxacin f-2(physical mixing) solid dispersion

S.NO	Time	OD	Amount of drug dissolved	%Drug dissolve	%Drug remaine	Log% Drug remained

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				d	d	
1	0	0	0	0	100	2
2	5	0.206	88.7	89.17	10.83	1.034
3	10	0.219	94.3	94.8	5.2	0.716
4	15	0.222	100	-	-	-

Table 8: kinetic profile of ciprofloxacin f-3 (cogrinding) solid dispersion

S.NO	Time	OD	Amount of drug dissolved	%Drug dissolved	%Drug remained	Log% Drug remained
1	0	0	0	0	100	2
2	5	0.213	88.7	74.89	25.11	1.4
3	10	0.232	97.38	91.72	8.28	0.918
4	15	0.23	99.04	100	0	-

Table 9 : kinetic profile of ciprofloxacin f-4 (kneading method) solid dispersion

S.NO	Time	OD	Amount of drug dissolved	%Drug dissolved	%Drug remained	Log% Drug remained
1	0	0	0	0	100	2
2	5	0.199	85.69	85.77	14.23	1.153
3	10	0.21	90.43	90.52	9.48	0.976
4	15	0.226	97.32	100	2.59	0.413

Table 10:kinetic profile of ciprofloxacin f-5 (solvent evaporation method) solid dispersion

S.NO	Time	OD	Amount of drug dissolved	%Drug dissolved	%Drug remained	Log% Drug remained
1	0	0	0	0	100	2
2	5	0.183	78.8	94.24	25.7	1.41
3	10	0.201	96.52	100	5.675	0.754

Table 11: Assay of Ciprofloxacin

S.NO	Formulation	Drug content	Practical yield
1	F1	94 mg	93
2	F2	89.8 mg	91.6
3	F3	90.72	91.03
4	F4	90.28	91.33
5	F5	93.31	94.18

Improvisation: As pure drug has shown poor dissolution property, in order to enhance the dissolution rate we used different methods for preparing solid dispersions.

Table 12: Dissolution parameters

S.NO	TRAILS	ZERO ORDER				FIRST ORDER		
		PD 10	T50	Regression	Ko	Slope	R	K1
		(%)	(min)	(R)	(mg/ml)	(b)		(min^{-1})
1	F-1	88.25	4	0.898	1.88	0.0917	0.9942	0.087
2	F-2	94.8	3.3	0.982	4.79	0.128	0.9608	0.022
3	F-3	100	3	0.992	2.73	0.108	0.998	0.077
4	F-4	90.52	3.5	0.899	0.762	0.0987	0.9702	0.126
5	F-5	100	3	0.991	10	0.1246	0.9995	0.55

Table 13: Dissolution release data

Sl no	TIME min	% DRUG DISSOLVED				
		F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	5	83.97	88.7	74.89	85.77	94.24
3	10	81.41	94.3	91.72	90.52	100
4	15	91.72	100	100	100	-
5	20	97.75	-	-	-	-
6	30	100	-	-	-	-

Fig 1: Dissolution Apparatus

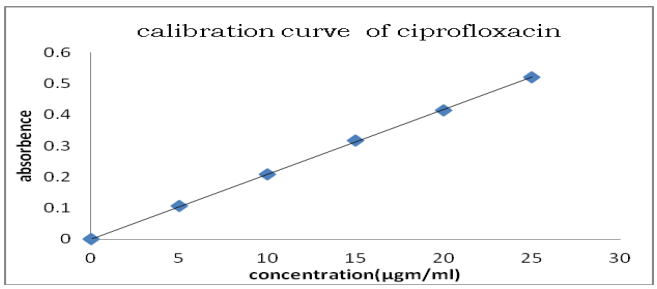

Fig 2: calibration curve for estimation of ciprofloxacin

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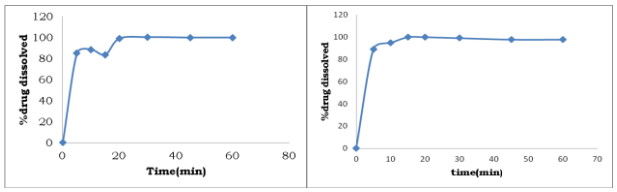

Fig 3: zero order kinetic profile of ciprofloxacin f-1(pure drug)

Fig 4: zero order kinetic profile of ciprofloxacin f-2(physical mixing) solid dispersion.

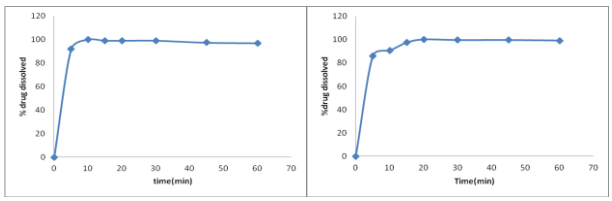

Fig 5: zero order kinetic profile of ciprofloxacin f-3 (cogrinding) solid dispersion

Fig 6: zero order kinetic profile of ciprofloxacin f-4 (kneading method) solid dispersion

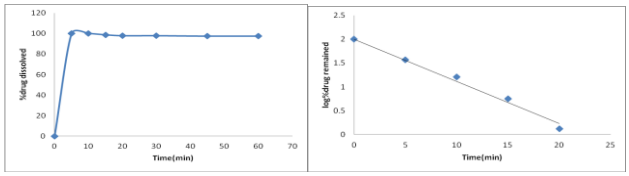

Fig 7: zero order kinetic profile of ciprofloxacin f-5 (solvent evaporation method) solid dispersion

Fig 8: first order kinetic profile of ciprofloxacin f-1(pure drug)

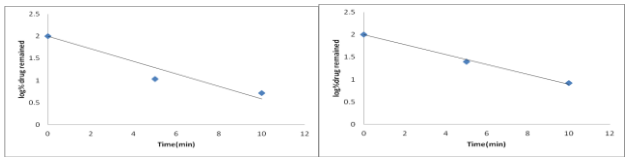

Fig 9: first order kinetic profile of ciprofloxacin f-2(physical mixing) solid dispersion.

Fig 10; first order kinetic profile of ciprofloxacin f-3 (cogrinding) solid dispersion

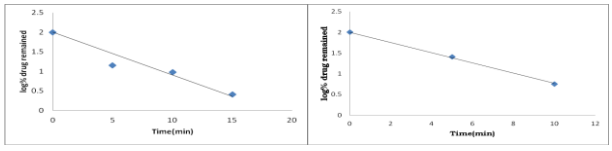

Fig 11: first order kinetic profile of ciprofloxacin f-4 (kneading method) solid dispersion.

Fig 12: first order kinetic profile of ciprofloxacin f-5 (solvent evaporation method) solid dispersion

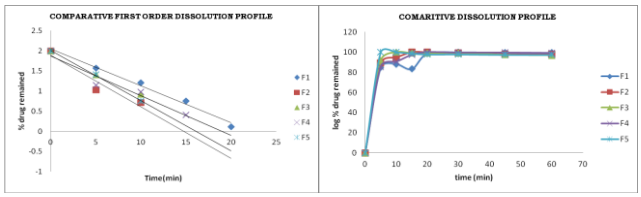

Fig 13: comparative first order dissolution profile

Fig14: comaritive dissolution profile

Trial -2

In this trail solid dispersion of drug was prepared by using Croscarmelose sodium as a disintegrant in the ratio of 1:1 and by using Physical mixing method. Maximum drug release was observed at time 15 min.

Improvisation: Further this formula was optimized for enhancing the drug release by using other technique.

Trial-3

In this trail solid dispersion of drug was prepared by using Croscarmellose sodium as a disintegrant in the ratio of 1:1 and by using Co–grinding method. Maximum drug release was observed at time 15 min.

Improvisation: Further this formula was further optimized for enhancing the drug release by using other technique.

Trial-4

In this trail solid dispersion of drug was prepared by using Croscarmellose sodium as a disintegrant in the ratio of 1:1 and by using kneading method. Maximum drug release was observed at time 20 min.

Improvisation: Further this formula was further optimized for enhancing the drug release by using other technique.

Trail-5

In this trail solid dispersion of drug was prepared by using Croscarmellose sodium as a disintegrant in the ratio of 1:1 and by using Solvent evaporation method. Maximum drug release was observed at time 10 min.

Hence the trial 5 which was prepared by using Croscarmellose sodium and drug by the ratio of 1:1 by using solvent evaporation was found to be optimized formula.

4. CONCLUSION

This study was undertaken with an aim to formulate an Anti-Biotic drug in the form solid dispersion to overcome the poor solubility drawback of the drug. The selected Antibiotic agent was Ciprofloxacin. The drug Ciprofloxacin is having poor solubility in the

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water, under class 2 of BCS of classification of drug its solubility was tried to increase by formulating in the form of solid dispersion with polymer by using various techniques. Solid dispersions were prepared by using the Crosscarmelose sodium as a disintegrant in 1:1 ratio of different techniques.

Among the four different techniques used for preparation o solid dispersions solvent evaporation technique has shown the increase in dissolution rate that is the Trail-5 was found to have a faster solubility and dissolution property which was prepared by using Croscarmellose sodium as a disintegrant in the ratio of 1:1. Hence finally it was concluded that Trail-5 as an optimized formula with an increased rate of dissolution rate and solubility. Trail 5 which is prepared by using drug and disintegrant ratio of 1:1 ratio by using solvent evaporation techniques.

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