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Research Article

Enhancement of Dissolution Rate of Cefixime Trihydrate by Using Various Solid Dispersion Techniques

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Abstract: Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. There are different approaches which can be used for increasing the dissolution of the poorly soluble drugs. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction. The solubility of Cefixime Trihydrate is- soluble in methanol but insoluble in water. Cefixime Trihydrate is absorbed orally as 40 – 50% and 50% excreted unchanged in Urine because of poor solubility of Cefixime Trihydrate it is prepared as sold dispersions by using various techniques like Physical mixing, Co – grinding method , kneading technique and solvent evaporation technique. The main objective is to formulate a drug product as immediate release oral solid dosage form of Cefixime Trihydrate solid dispersion system which is considered to be stable, robust quality and enhanced dissolution rate. Thus kinetic study and dissolution study of the Formulated solid dispersions among the four different techniques used for preparation of 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. Thus by this we can overcome the poor solubility drawback of the drug Cefixime Trihydrate.

Keywords: Solid dispersions, Cefixime Trihydrate, Croscarmelose sodium, Solvent evaporation technique.

Introduction

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability rather than the limited permeation through the epithelia and the formulation of poorly soluble drugs for oral delivery now presents one of the major challenges to formulation scientists. Solid dispersion was introduced in the early 1970s, refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. There are different approaches which can be used for increasing the dissolution of the poorly soluble drugs.

Thus the term solid dispersion can be defined as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”[1]. Solid dispersion is a promising approach to improve the dissolution and bioavailability of hydrophobic drugs. The preparation and storage conditions of solid dispersions are crucial since changes may alter the dissolution characteristics of the active ingredients. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction.

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. Thus in this article we have selected Cefixime Trihydrate. The solubility of Cefixime Trihydrate is- soluble in methanol but insoluble in water. Cefixime Trihydrate is absorbed orally as 40-50% and 50% excreted unchanged in Urine. Its serum half-life is 3-4 hours. Because of poor solubility of Cefixime Trihydrate it is prepared as sold dispersions by using various techniques like Physical mixing, Co – grinding method , kneading technique and solvent evaporation technique. Its limitation is drug absorption which has poor bioavailability of drug.

When the active ingredient can be delivered as GIT orally, it first dissolved in intestinal fluids before it reach to systemic circulation. Therefore a drug having poor aqueous solubility will typically exhibit in dissolution rate limitation and absorption and a drug with poor membrane permeability will exhibit the permeation rate absorption limited. So that oral bioavailability of drugs can be improved by the enhancing solubility and dissolution rate of poorly water soluble drugs, and another is enhancing the permeability of poor permeable drugs.

Solid dispersions can be prepared by the various methods those are deals with the mixing of matrix and a drug, preferably on a molecular level, while the matrix and drug are generally poorly miscible by solvent evaporation method[3], Fusion method/melting method[4], Hot melt extrusion[5], Supercritical fluid technology (SCF)[6], Dropping method[7], Electrostatic Spinning Method[8], Co-precipitation method[9]. Advantages of solid dispersion includes particles with reduced particle size have high surface area, resulting in an increased dissolution rate and, consequently,

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improved bioavailability[2]; drug solubility is related to the drug wettability which can be improved by solid dispersions; Particles in solid dispersions have been found to have a higher degree of porosity results in a higher dissolution rate. The main objective of present investigation is to design and evaluate the Enhancement of dissolution rate of cefixime trihydrate by using various solid dispersion techniques.

Materials and Methods

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

Formulation of tablets with different solid dispersion methods

Formulation 1 - PURE DRUG (100mg)

Physical Mixing:

Accurately weighed required amount of Cefixime Trihydrate 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. [Formulation 2 – DRUG: POLYMER (1:1) Croscarmelose sodium.]

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 [Formulation 3 - DRUG: POLYMER (1:1) Croscarmelose sodium]

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 4 – 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 [Formulation 5– DRUG: POLYMER (1:1) Croscarmelose sodium]

Evaluation of prepared solid dispersions Percentage yield:

Percentage practical yield were calculated to know about percent yield or efficiency of anyMethod, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation

$$\text{Percentage yield} = \frac{\text{Practical mass of Solid dispersion}}{\text{Theoretical mass (Drug + carrier)}} \times 100$$

Drug content

The Physical mixture and solid dispersion equivalent to 50 mg of drug were taken and dissolved separately in100 ml of phosphate buffer pH 7.2. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 288 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as follows

$$\% \text{ drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Results and Discussion

Tables 1-6 shows the trails done by using the formulations F1 –F5 of Cefixime trihydrate which were prepared by solid dispersion technique using Croscarmelose sodium as a disintegrant in the ratio of 1:1, by using Physical mixing method, Co–grinding method, kneading method and by Solvent evaporation method. As pure drug has shown poor dissolution property and other techniques has shown maximum drug release at time 15 to 20 min but by using Solvent evaporation method maximum drug release was observed. As this trails were performed for the enhancement of dissolution rate of cefixime trihydrate by using Croscarmellose sodium and drug by the ratio of 1:1. Thus the technique solvent evaporation of solid dispersion was found to be optimized formula.

***In-vitro* release studies:**

All the five formulations were subjected for the in vitro dissolution studies apparatus USP-II. The samples were taken at hourly intervals and analyzed at 256nm. Cefixime Trihydrate tablet formulation F1 to F5 were formulated with various methods of solid dispersions. In vitro dissolution data were treated using zero order, first order. The kinetic plots were given in graph 1 and 2. The kinetics values

regression coefficient (r), slop (n), rate constant are shown in Table-7 & 8.

Table.1: Kinetic Profile of Cefixime Trihydate 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	1.070
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.2: Kinetic Profile of Cefixime Trihydate 2 (Physical Mixing) 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	0.206	88.70	89.17	10.83	1.034
3	10	0.219	94.30	94.80	5.2	0.716
4	15	0.222	100	-	-	-

Table. 3: Kinetic Profile of Cefixime Trihydate 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	88.70	74.89	25.11	1.4
3	10	0.232	97.38	91.72	8.28	0.918
4	15	0.230	99.04	100	0	-

Table. 4: Kinetic Profile of Cefixime Trihydate 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	0.210	90.43	90.52	9.48	0.976
4	15	0.226	97.32	100	2.59	0.413

Table. 5: Kinetic Profile Of Cefixime Trihydate 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	78.80	94.24	25.70	1.41
3	10	0.201	96.52	100	5.675	0.754

Table.6: Assay of Cefixime Trihydrate

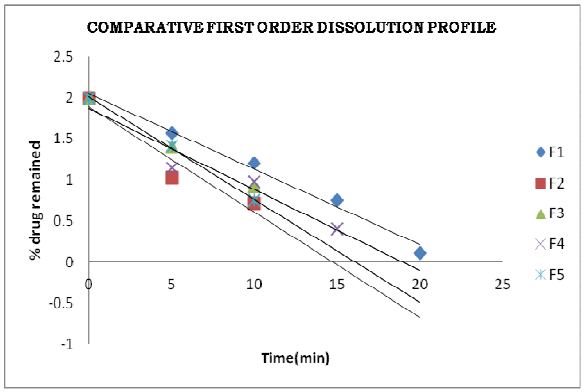
S.NO	Formulation	Drug content	Practical yield
1	F1	94 mg	93
2	F2	89.8 mg	91.6
3	F3	90.72	91.03
4	F4	90.28	91.33
5	F5	93.31	94.18

Table.7: Dissolution Parameters

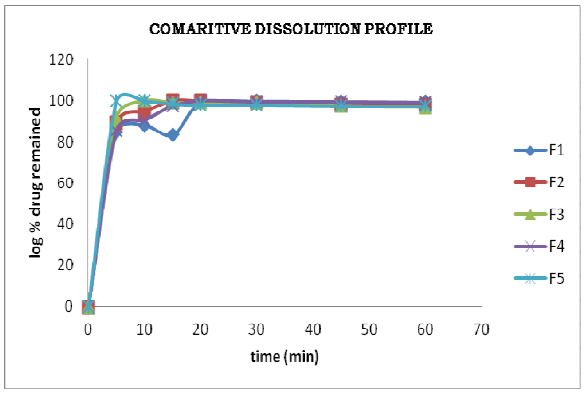
S.NO	TRAILS	ZERO ORDER				FIRST ORDER		
		PD10 (%)	T50 (min)	Regression (R)	Ko (mg/ml)	Slope (b)	R	K1 (min^{-1})
1	F-1	88.25	4	0.898	1.88	0.0917	0.9942	0.087
2	F-2	94.8	3.3	0.982	4.79	0.128	0.9608	0.022
3	F-3	100	3	0.992	2.73	0.108	0.998	0.077
4	F-4	90.52	3.5	0.899	0.762	0.0987	0.9702	0.126
5	F-5	100	3	0.991	10	0.1246	0.9995	0.55

Table.8: Dssolution Data

S.NO	TIME min	% DRUG DISSOLVED				
		F1	**F2**	**F3**	**F4**	**F5**
1	**0**	0	0	0	0	0
2	**5**	83.97	88.70	74.89	85.77	94.24
3	**10**	81.41	94.30	91.72	90.52	100
4	**15**	91.72	100	100	100	-
5	**20**	97.75	-	-	-	-
6	**30**	**100**	-	-	-	-



Graph.1: Comparative First Order Dissolution Profile



Graph.2 Comaritive Dissolution Profile

Conclusion

This study was undertaken with an aim to formulate an Antibiotic drug in the form solid dispersion to overcome the poor solubility drawback of the drug. The selected Antibiotic agent was Cefixime Trihydrate. The drug Cefixime Trihydrate is having poor solubility in the 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 Croscarmelose sodium as a disintegrant in 1:1 ratio of different techniques.

Among the four different techniques used for preparation on 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 technique.

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