Available online on 15.12.2018 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Novel application of mixed solvency concept in the development of oral liquisolid system of a poorly soluble drug, cefixime and its evaluation

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ABSTRACT

Application of mixed solvency has been employed in the present research work to develop a liquisolid system (Powder formulation) of poorly water soluble drug, cefixime (as model drug). **Material and Methods:** For poorly water soluble drug cefixime, combination of solubilizers such as sodium acetate, sodium caprylate and propylene glycol as mixed solvent systems were used to decrease the overall concentration of solubilizers required to produce substantial increase in solubility and thereby resulting in enhanced drug loading capacity of cefixime. The procured sample of cefixime was characterized by melting point, IR, UV and DSC studies. Stability studies of liquisolid system of cefixime were performed for two months at room temperature, 30˚C and 40˚C. All the formulations were physically, chemically, and microbiologically stable. **Conclusion:** Mixed solvency concept has been successfully employed for enhancing the drug loading of poorly water soluble drug, cefixime.

Keywords: Solubility, cefixime, liquisolid system, mixed solvency concept.

Article Info: Received 13 Oct 2018; Review Completed 19 Nov 2018; Accepted 23 Nov 2018; Available online 15 Dec 2018

Cite this article as:

Agrawal R, Maheshwari RK, Novel application of mixed solvency concept in the development of oral liquisolid system of a poorly soluble drug, cefixime and its evaluation, Journal of Drug Delivery and Therapeutics. 2018; 8(6-s):5-8

DOI: http://dx.doi.org/10.22270/jddt.v8i6-s.2167

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1. INTRODUCTION

The technique of "Liquisolid compact" is a type of powdered solution technology [1-5]. It is a novel method to improve the *in vivo* solubility of poorly water soluble drugs. The basic concept here is to convert the liquid form of drug into free flowing readily compressible powder. Here the liquid drug, drug solution, suspension or emulsion is converted into free flowing powder by simply adsorbing it on an inert carrier with addition of various excipients such as binder and others required to prepare the tablet and then the mass is compressed to tablet.

Components [6]

Drug: Drugs of all class of BCS system of classification

Non-volatile solvent: It must be inert, hydrophilic, having low viscosity and high boiling point. Eg: Polyethylene Glycols (liquids), Propylene Glycol, Glycerol.

Carrier: These are material with high porosity and a wide surface area which serves as a base to adsorb the liquid form of drug. Eg: MCC, Methyl Cellulose, Ethyl Cellulose, and Starch.

Coating material: These are fine materials of size range10nm-450nm. These should be highly adsorptive to cover the carrier particle to make it look dry. Eg: Aerosil 200, Silica, and Syloid.

Disintegrants, **Lubricants, Glidants** [6]

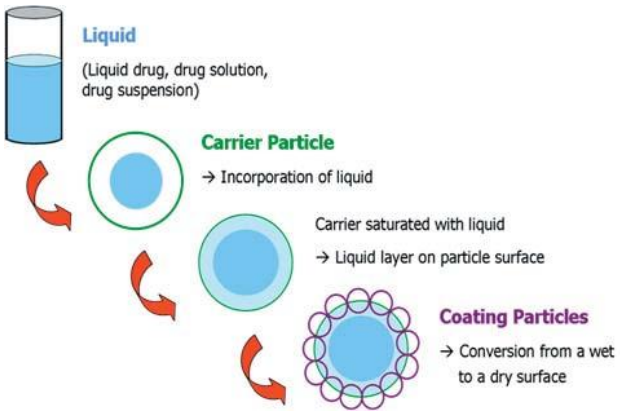

Figure 1: Molecular level diagram

There is an absolute necessity of solubility of an amount of drug desired as per the strength of dosage form to be present in the minimum amount of the solvent to be used as solution. For this purpose a suitable solvent or solvent

system is to be selected. The main objectives of the present work are to develop a suitable solvent system to enhance the drug loading capacity by enhancing the solubility of drug in nonvolatile solvent by using mixed solvency concept in liquisolid system, increase the flow property by reducing the required volume of nonvolatile solvent.

As per the mixed solvency concept [7], each and every substance present in the universe has got solubilizing property and each substance is a solubilizer. Each and every weaker solvent (for a solute) can be made a strong solvent by proper selection of solubilizers. A concentrated aqueous solution containing various water soluble substances may act as good solvent for poorly water soluble drugs. By combining various excipients, additive and synergistic solvent actions are expected which has advantage of reducing the toxicities. For a desired solubility enhancement, a single solubilizer may prove toxic for human being but the combination of different excipients in safe smaller concentrations solves the problem of toxicity for same desired solubility of drug. The solubilities of a large number of poorly water soluble drugs have been enhanced by the mixed solvency concept.[8-23]

Also, use of multiple solubilizers reduces the amount of individual solubilizers, rendering it towards their safe use. Moreover, it also emerges as a tool to increase the drug loading in the same solvent, earlier having less room for drug and skipping the use of alternate solvent which is more likely of organic nature. After the use of mixed solvency concept, the solvent emerges as mixed solvent system.

Cefixime [24, 25] is a broad-spectrum, 3rd-generation cephalosporin antibiotic which is derived semi-synthetically from the marine fungus Cephalosporium acremonium with antibacterial activity. Cefixime inhibits the bacterial cell wall synthesis by disrupting peptidoglycan synthesis, resulting decrease in the cell wall stability and bacterial cell lysis.Cefixime is stable in the presence of a variety of beta-lactamases. Cefixime is more active against gram-negative bacteria and less active against gram-positive bacteria compared to second-generation cephalosporin.

Application of the mixed solvency concept has been used to enhance the drug loading capacity in liquisolid system and to increase the flow property by reducing the required volume of nonvolatile solvent and enhance the solubility of drug in nonvolatile solvent. Cefixime was selected as model poorly water soluble drug for exploring the mixed solvency concept to enhance the solubility and hence to enhance the release rate of drug.

2. MATERIALS AND METHODS

2.1 Materials: Cefixime was obtained as a gift sample from Schon pharmaceutical limited, Indore.

2.2 Preparation of calibration curve of cefixime in demineralized water:

50 mg of pure drug was accurately weighed and transferred into a 500 ml volumetric flask. It was dissolved with 300 ml of demineralized water and volume was made upto 500 ml with demineralized water to obtain stock solution of 100µg/ml. From the stock solution, appropriate dilutions were prepared in the range of 5-25µg/ml. Absorbances of resulting solutions were noted at 288 nm against demineralized water. The data were graphically represented in Figure 2.

2.3 Determination of interference of excipients in the spectrophotometric estimation of cefixime:

For determination of interference of additives in the spectrophotometric estimation of cefixime, the absorbances of the standard solutions of cefixime were determined in DM water alone and in the presence of fairly large concentrations of solubilizers. For this, 50 mg of drug was dissolved in 450ml of demineralized water in a 500 ml volumetric flask and shaken until a clear solution was formed and then the volume was made upto 500 ml with demineralized water to make stock solution of drug (100µg/ml). Then, 10 ml of the above solution was taken and diluted upto 50ml with demineralized water. This gives a solution of 20µg/ml. Likewise, excipient solution was prepared by dissolving 2000mg of each solubilizers in 50ml distilled water and volume was made upto 100ml with demineralized water, to obtain 20,000µg/ml stock solution. From the above solution, 20ml of stock solution of drug (100µg/ml) and 10ml of stock solution of excipient (20,000 µg/ml) was taken and volume was made upto 100ml with demineralized water. The absorbances were recorded against respective reagent blank at 288nm and results are shown below in table 2. A UV –visible recording spectrophotometer (shimadzu 1700) with 1 cm matched silica cells was employed for spectrophotometric determination.

2.4 Drug excipient interaction studies:

The compatibility of the drug with the excipient was assessed by drug-excipient interaction studies. The drug was mixed with excipient in 1:1 ratio in separate clear glass vials which were then properly sealed and kept undisturbed at different temperature conditions; at room temperature, and in refrigerator for a period of one month. After every week, vials were withdrawn and contents were observed for any change in their physical appearance.

2.5 Solubility studies:

In order to carry out the equilibrium solubility of cefixime in various blends , 4ml of each blend was taken in 10 ml vials and then excess amount of drug was added in each vials .Then vials were subjected to continuous shaking in water bath at room temperature in incubator shaker for 24hours. All vials were containing suspension of drug. Then vials were kept undisturbed for 12 hours. After filtration through filter paper, the filtrates were suitably diluted with demineralized water and absorbances were measured at 288nm.Then, equilibrium solubility of drug in each blends were calculated by using calibration curve. Results are shown in table 3.

2.6 Formulation development of Liquisolid system (Powder):

Based on the solubility studies, liquisolid system were prepared using blend [25% Sodium Caprylate+12.5% Sodium Acetate] was taken (4 ml) and accurately weighed 2000 mg drug was dissolved in it by mixing it in the cleaned and dried pestle mortar by trituration yielding a yellow colored clear solution. To the solution, gross amount of Starch 1500 (36,000 mg) and Tricalcium phosphate (28,000 mg) as carriers were added and allowed to adsorb the drug. The mixture was then triturated to allow and check the uniform mixing and adhesiveness of the powder and the remaining amount of carrier was again added to reduce the adhesiveness.

Table 1: Formula for liquisolid system of cefixime:

Batch No.	Carrier	Drug added (mg)	Amount of carrier used (mg)	Volume of blend used (ml)	Net weight (mg)
LSC-01	Tricalcium phosphate	2000	28,000	4	31,500
LSC-02	Starch 1500	2000	36,000	4	43,500

2.7 Stability studies: Liquisolid systems of cefixime of two different formulations were kept at different storage conditions. Formulations were kept at room temperature, at 30°C and at 40°C.

3. Evaluations of Liquisolid system:

3.1Thin Layer Chromatography (TLC) analysis: TLC analysis was done to identify any drug-solubilizer interaction (table 4). Methanol was used as solvent for sample preparation for TLC of drug.

3.2 Flow property

Tapped density is considered as a basic parameter to judge the flow behavior and a tool to judge the compressibility of the powders. It determines the efficiency of compression and is responsible for affecting various parameters.

The tapped density of the liquisolid system thus developed was calculated by Electro lab Tap density Tester by USP II method

Weight of sample = 27.66 gm

Initial Volume (V_0) = 67mL

Volume after 500 tapping (V_1) = 62 ml

Volume after 750 tapping (V_2) = 61ml

Volume after 1250 tapping (V_3) = 61 ml

4.0 RESULTS AND DISCUSSION

4.1 Preparation of calibration curve of cefixime in demineralized water:

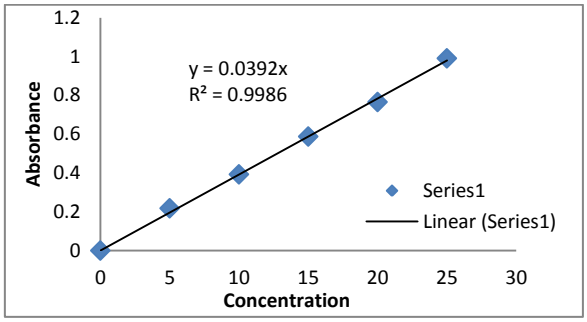

Figure 2: Calibration curve of cefixime in demineralized water

4.3 Drug-solubilizers interference studies in the spectrophotometric estimation of cefixime: Observing the results of drug-solubilizers interference study, it was concluded that there was no interference in UV spectrophometric analysis of cefixime due to excipients.

Table 2: Drug-solubilizers interference studies in the spectrophotometric estimation of cefixime

S.No.	Cefixime and/or Excipient	Drug concentration (µg/ml)	Solubilizer concentration (µg/ml)	Absorbance at 288nm	Interference
1	Cefixime	20	---	0.737	---
2	Cefixime + sodium acetate	20	2000	0.734	NO
3	Cefixime + sodium aprylate	20	2000	0.736	NO

4.4 Drug solubilizers incompatibility studies: Observing the results of drug-solubilizers imcompatibility study it was concluded that there was no physical incompatibility between drug and selected formulation solubilizers.

4.5 Formulation development:

4.5.1 Solubility studies: Maximum increase in solubility of cefixime was observed in **Blend F (25% S.C. + 12.5% S.A)** so this blend was selected for preparing the formulation of liquisolid system of cefixime.

Table 3: Solubility studies of cefixime in various aqueous solutions of solubilizers

S.No.	Blend	Composition of blends	Solubility (mg/ml)	Solubility (%w/v)
1	A	20% Sodium caprylate	320.25	7.15
2	B	20% Sodium caprylate, 10% β Cyclodextrin	160.45	3.57
3	C	15 %Sodium caprylate, 15 % Sodium acetate	250.56	4.46
4	D	10% Sodium caprylate, 10% Sodium acetate	190.32	4.24
5	E	1:1 PEG 400 & Propylene glycol, 15% Sodium caprylate	354.25	7.91
6	F	25% Sodium caprylate, 12.5% Sodium acetate	476.67	10.64
7	G	20% Sodium caprylate, 5% PVP K_{25}	370	8.26
8	H	10% Sodium acetate, 5% PVP K_{25}	325	7.25

4.5.2 Stability studies: Stability studies of Liquisolid system of cefixime were performed for two months at room temperature, 30˚C and 40˚C and percent drug remaining for first formulation (Batch First) at room temperature was 97.07% and at 30˚C was 98.88% and at 40˚C was 96.45%. Percent drug remaining for second formulation (Batch Second) at room temperature was 97.89%, at 30˚C was 97.44% and at 40˚C was 96.32%. The results of stability studies of cefixime liquisolid system (powder) were reasonably good.

4.6 Evaluations:

4.6.1 TLC analysis: From TLC study, it is clear that there is no significant change in R_f value indicating that there were no interactions between drug and solubilizers.

4.6.2 Densities:

Tapped density (ρ_T) =0 .452gm/ml

Bulk density (ρ_B) = 0.413 gm/ml

Table 4: TLC analysis of pure cefixime and its formulations

S. No.	Solvent system	R_f value
1.	Drug in methanol	0.45
2.	Drug in blend F	0.41

5. CONCLUSION

Mixed solvency concept has been wisely used to develop a fast release formulation of poorly water soluble drug, cefixime by liquisolid technique using non-volatile solvent such as propylene glycol and various blend of solubilisers such as sodium caprylate and sodium acetate for enhancing the solubility of drug and thereby enhancing the drug loading of formulation.

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