International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

STUDIES ON EFFECT OF HUMIDITY ON PERFORMANCE OFCO-CRYSTALS OF MEFLOQUINE HYDROCHLORIDE AND ITS TABLET DOSAGE FORM.

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ABSTRACT

Cocrystallization of pharmaceutical cocrystals is alternative to salts, solvates and polymorphs which helps to modify the physicochemical properties of API during manufacture of any dosage form. Therefore one can modify the physicochemical properties of the API and bulk drug material by maintaining the intrinsic activity of drug. The delivery of drug in cost effective manner to patients largely depend upon the physicochemical properties in it's solid state.

Key words: Crystal engineering, Co-crystals, Solution crystallization, Antisolvent method, MEF and stability.

INTRODUCTION

Co-crystals are usually defined as multiple component structures which interact by hydrogen bonding or weak intermolecular interactions. It consist of crystalline solid which incorporates two neutral molecules i.e. API and co-crystal former. Co-crystal former is usually drug or an excipient.

Co-crystallization helps to modify the properties of API thus by enhancing the solubility, hygroscopicity and compacting behavior of the formulation. Co-crystallization is most widely used technique in solid pharmaceutical substance. Therefore it is classified into co-crystal anhydrates, co-crystal hydrates (solvate), hydrates and anhydrates of co-crystal salts.

According to BCS classification the API belonging to class II and IV have always helped in enhancing the solubility. Hence, one such technique is Co-crystallization [1]. Stability is defined as ability of substance to remain unchanged over stated conditions of storage and use.Stability plays an important role incase of every formulation. The primary concern of stability for any formulation is patient well being. If stability is not maintained it may cause harm to the health of the patients ultimately leading to death. To avoid this stability guidelines are made by the regulatory agencies before approval new drug in the market [2]. Stability is considered to Co-crystals too therefore incase of co-crystals it is necessary to ensure chemical stability, solution stability, relative humidity stability and thermal stability [3].

Mefloquine hydrochloride its IUPAC Name (2,8 bis[triflurомethyl)quinolone-4-yl]-Piperidyl-2-yl methanol). Mefloquine hydrochloride is an antimalarial drug which belongs to class of quinoline methanol. It is used as blood schizonticide for combacting drug resistant falciparum malarial infections. It belongs to BCS class II i.e. high permeability and low solubility. In earlier literature only co-crystals has been formulated and evaluated in an tablet dosage form but it has been reported that mefloquine hydrochloride shows an polymorphism when exposed to high humidity [4].

The present investigation may study the effect of humidity on transformation or any phase transition of co-crystals when exposed to high humidity conditions.

MATERIALS AND METHODS

Mefloquine hydrochloride was procured from Mcleod pharmaceuticals. The chemicals and solvents used were of analytical grade and procured from Lobachemie Mumbai.

Methods of preparation of Co-crystals

Preparation of physical mixtures

Physical mixtures were prepared by mixing mefloquine and coformers in the ratio of 1.1 and then sieved [5].

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Preparation of co-crystals by antisolvent addition technique

In this method drug and conformer is dissolved in ethanol 20ml with moderate stirring. This solution is filtered by whatman filter paper. Then addition of d/w is made to the above solution with constant stirring and finally the co-crystals are dried in dessicator.

Preparation of co-crystals by solution crystallization technique

Coformer and Mefloquine in 1:1 molar ratio were dissolved in 20 ml ethanol with sonication. The saturate solution was kept overnight to evaporate the solvent. The crystals were obtained after evaporation of ethanol; crystals were allowed to dry in the air [6].

Evaluation and Solid state characterisation of Co-crystals

Saturation solubility of drug and prepared co-crystals in S.G.F {ph 1.2}and in DW.

For saturation solubility an excess quantity of MFL or prepared co-crystals were placed in vials containing 10ml of S.G.F {ph 1.2}and in DW. The vials were agitated in incubator shaker for 24hrs at (100 agitations/min).Then solution was filtered by membrane filter and analyzed by UV spectrophotometer to determine the drug dissolved in S.G.F.

Determination of drug content

For drug content, prepared crystals were triturated with simulated gastric fluid (SGF) (pH 1.2) and volume was made up to 100 ml with the same filtered and analyzed by spectrophotometer.

Fourier Infrared spectroscopy

Infrared characterization was done by using the equipment (Shimadzu) spectrophometer. The spectrum is usually recorded in the wavelength region of 4000-400cm^{-1}.In this the sample is dispersed alone or mixture of cocrystals in KBr and compressing into discs by applying a slight pressure of 5 t for 5min in hydraulic press and finally the pellets are placed in light path for the recording of spectrum.

Powdered X-Ray Diffraction

The XRD patterns of pure drug and the optimized crystals formulation were recorded using Philips analytical X-ray diffractometer.

Formulation and Evaluation of Tablets

Preparation of tablets from co-crystals

Prepared co-crystals and pure MFL were formulated by using microcrystalline cellulose (pH102) as bulking agent with (PVP- K30) as a binder.

Compression of co-crystals into tablets by using different coformers

After co-crystals preparation, co-crystals equivalent to 250 mg of mefloquine hydrochloride were weighted and tablets were compressed on single stroke tablet compression machine (Dolphin, Mumbai, India) [7].

Thickness and Diameter

To measure thickness and diameter vernier calliper is used.

Tablet hardness

Usually tablet hardness is measured to resist breaking during normal handling and should sufficiently disintegrate properly after swallowing. This test is performed using Monsanto hardness tester.

Friability

Roche friabilator was used for testing the friability.

% Friability =

$$\frac{\text{Initial weight of tablets- final weight of tablets} \times 100}{\text{Initial weight}}$$

Weight variation test

The weight of tablet is measured to ensure that a tablet contain the proper amount of drug in it. 20 tablets are selected randomly and weighed. Average weight of the tablet was determined. Not more than the two of the individual weights deviate from the average weight by more than 5 % percentage deviation.

Disintegration Test

For most of the tablets the first most important step towards solution is breakdown of the tablet into smaller particles or a granules, a process known as disintegration. In this test the assembly is suspended in liquid medium containing 900ml of dissolution media. The volume of liquid is adjusted in such a way that liquid is maintained at the highest point 25mm below the surface of the liquid and lower point at least 25mm above the bottom of the beaker.A thermostat arrangement is made for heating and temperature is maintained at $37^0C \pm 0.2^0C$.Tablets gets disintegrate into media.

Dissolution of Co-crystals

In-vitro dissolution studies of Mefloquine and prepared tablets of cocrystals were performed inUSP Type II dissolution test apparatus. The dissolution profile of Mefloquine hydrochloride tablet and its cocrystal tablet were determined in 900 ml of simulated gastric fluid pH 1.2 at 100rmp and thermostatically controlled bath for $37^oC\pm 0.5^0C$.Samples are withdrawn at specific time interval and filtered. After filtration samples are diluted and absorbance is taken on UV [6].

Stability studies of co-crystals

Stability study for the samples were carried out in dessicator with salt solution. Reason behind the placing the samples in the dessicator with salt solution to maintain the humidity for the samples in desicator. The samples were kept in dessicator for a period of 45 days for stability studies. The samples were kept in an open container for

maximum exposure to humidity. In dessicator containing the saturated solution of sodium chloride. For stability study samples was analysed for appearance and drug content after 45 days [7].

Photomicrographs of Co-crystals

The photographs of pure drug, conformer and cocrystals were taken by using digital camera Under 10X magnification power. The pinch of powder formulation were sprinkled on to the Slide and photographs were taken under the 10X magnification power to determine the surface morphology of cocrystals.

RESULTS AND DISCUSSION

Formulation and Evaluation of Co-crystals

Saturation solubility of co-crystals in SGFpH (1.2)

The results of saturation solubility ofco-crystals revealed that co-crystals of benzoic acid prepared showed highest solubility in SGF of pH (1.2) than pure drug. The increase in solubility of benzoic acid co-crystal is due to complexation phenomenon in the solution and hydrogen bonding as compared to other coformers and drug [2, 3, 6].

Determination of percentage yield and Drug content

Co-crystals were prepared by various methods it involves inclusion of solvent. The percent yield of all co-crystals was found to be in the range of 81.45%-89.65%. The results of mefloquine content in prepared co-crystals were found to be in the range of 90.00-90.51% as mentioned in table 1 [2, 3].

Crystalline State Evaluation P XRD Analysis

Stability of Tablets after 45 days

The tablets are characterized for physical appearance and dug content after 45 days .

The XRD patterns of the pure drug is shown in fig2 with characteristic intense peaks of crystallinity at11.32º,14.10º,21.14º,25.37º and 32.15º (2θ)with peak intensities of 767,1750,454,715 and 420respectively indicating its crystalline nature. To determine the crystallinity in co-crystals it is usually done by comparing peak height with reference. The relative degree of crystallinity (RDC) of Mefloquine in co-crystals was calculated according to the equation. RDC= Isam/ Iref, whereas Isam is the peak height of the sample under investigation and Iref is the peak height at the same angle for the reference with the highest intensity.

Co-crystals Characterization

Fourier Transform Infrared spectroscopy

Toknow the possible interaction between the drug and the co-crystal formers IR spectroscopy is done. Pure Mefloquine hydrochloride peaks are shown in table [4, 5].

The dissolution studies shows enhancement in solubility for all co-crystals than pure drug this is because strength crystal lattice and salvation of co-crystal component.

Evaluation of Tablets

Tablets are prepared by direct compression method. Observations are shown in table4 .The % deviation in weights of tablets was ± 10% which is within the range according to IP.The hardness was within range of 4-5 kg/cm^2.The diameter was found to be in the range of Friability was to be found 0.32 – 0.53%. And all the tablets were disintegrated within 1-2 min [1].

The drug content is shown in table 5 as there is no considerable change after 45days and physical appearance is examined by naked eyes.

Table 1. IP standards for uniformity of weight for Tablets

Sr.No.	Average weight of tablet	Percentage deviation
1	80 mg. or less	± 10
2	80 mg. to 250 mg.	± 7.5
3	250 mg. or more than 250 mg.	± 5

Table 2. Percentage yield and Drug content

Formulation	% yield	Drug content
COASP	81.45%	90.17±0.17
COBENZ	84.86%	90±0.15
COGLU	85.44%	90.51±0.054
COOXAL	82.67%	90±0.15
COSALI	83.33%	90.17±0.17
COSU	89.65%	90.34±0.057

***All values are mean ± SD (n=3)**

Table 3. FTIR interpretation of MEF

Range	Absorption at cm^{-1}	Type of bond
3300-3500	3319	N-H stretching
2500-3100	2713	Weak interactions
1500-1600	1589	C-C
1200-1400	1307	C-N stretching

1140-1305	1172	C-F
1000-1300	1111	C-O
600-800	779	C-X

Table 4. Interpretation of co-crystals by PXRD

Sr.No.	Co-crystals	Angle(2θ)	RDC	CI
1	Aspartic acid co-crystals	14.10	0.577	57%
		25.37	0.727	72%
2	Benzoic acid co-crystals	14.10	0.582	58%
		25.37	0.390	39%
3	Glutaric acid co-crystals	14.10	0.537	53%
		25.37	0.639	63%
4	Oxalic acid co-crystals	14.10	0.241	24%
		25.37	0.577	57%
5	Salicylic acid co-crystals	14.10	0.453	45%
		25.37	0.73	73%
6	Succinic acid co-crystals	14.10	0.672	67%
		25.37	0.949	94%

Table 5. Tablet Properties

Tablets	Thickness(mm)	Disintegration time	Hardness(kg/cm^2)	%Friability
Aspartic acid	4.2 ± 0.18	1±0.63	4±0.57	0.48±0.054
Benzoic acid	4 ±0.16	1.3±0.64	5±0.59	0.32±0.051
Glutaric acid	4.2 ±0.18	1.2±0.62	4±0.57	0.35±0.052
Oxalic acid	4.1 ±0.17	1±0.63	5±0.59	0.40±0.050
Salicylic acid	4 ± 0.16	2±0.72	4±0.57	0.49±0.055
Succinic acid	4.3 ±0.19	1±0.63	5±0.59	0.53±0.060
Mefloquine hcl	4 ±0.16	2±0.72	4±0.57	0.34±0.056

***All values are mean ± SD (n=3)**

Table 6. Drug content of Tablets after 45 days

Formulation	Drug content Before stability	Drug content (after 45 days)
COASP	90.37±0.17	89.17±0.02
COBENZ	90±0.15	89±0.01
COGLU	90.51±0.054	89.51±0.03
COOXA	90.10±0.15	88±0.02
COSAL	90.27±0.17	89.17±0.03
COSU	90.54±0.057	89.34±0.02

Fig 1. Saturation solubility of co-crystals in S.G.FpH (1.2)

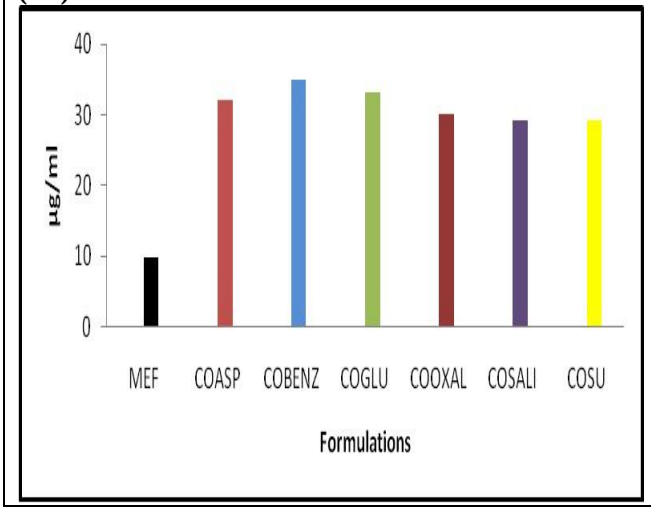


Fig 2. Overlay FTIR of a)MEF b)COASP c)COBENZ d)COGLU e)COOXAL f)COSALI g)COSU

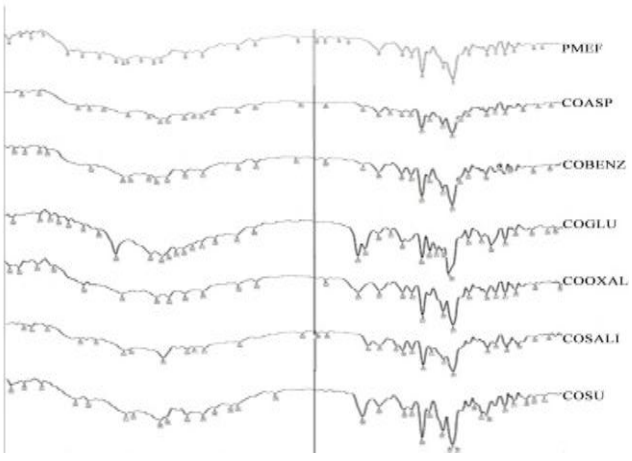


Fig 3. PXRD of MEF

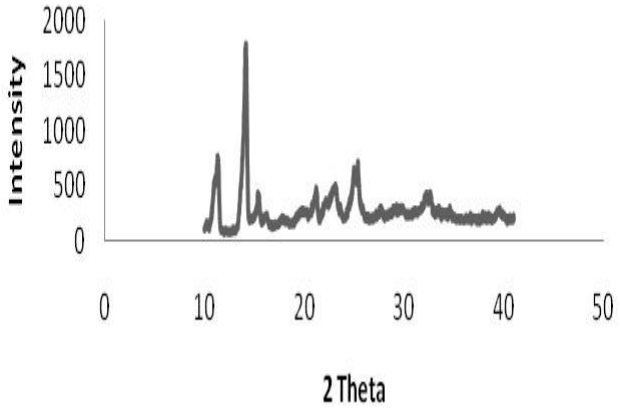


Fig 4. Overlay PXRD of a)MEF b)COASP c)COBENZ d)COGLU e)COOXAL f)COSALI g)COSU

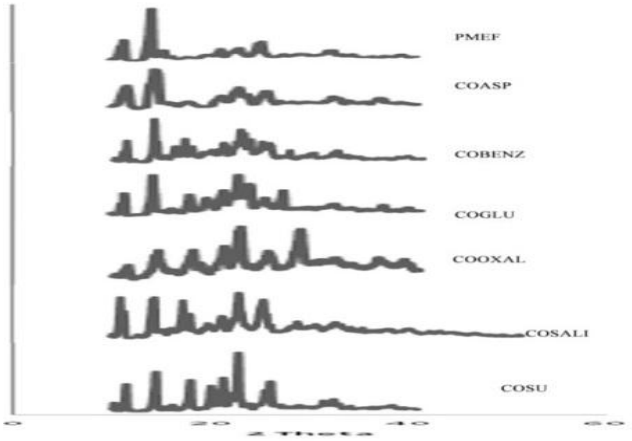


Fig 5. *In*-vitro dissolution study of Co-crystals and drug

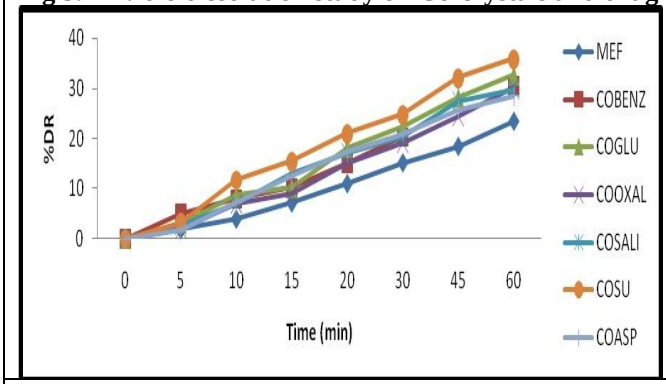


Fig 6. Photomicrograph of co crystals

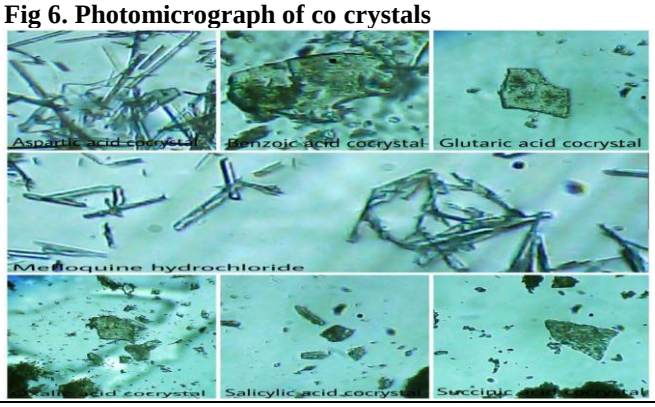
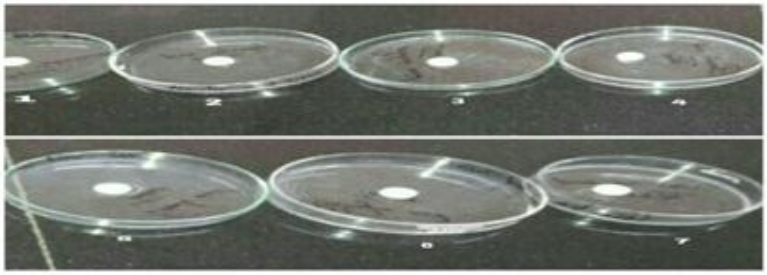


Fig 7



1. Mefloquine HCL tablet
2. Aspartic acid tablet
3. Oxalic acid tablet
4. Benzoic acid tablet
5. Glutaric acid tablet
6. Salicylic acid tablet
7. Succinic acid tablet

CONCLUSION

From the results we can conclude that co-crystals of mefloquine with dicarboxylic and amino acids as a coformer can improve the structural integrity of co-crystals which is confirmed by PXRD studies and it shows co-crystals were stable. No any issue of polymorphism has been observed.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

No interest

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