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SOLUBILITY ENHANCEMENT OF DICYCLOMINE USING SOLID DISPERSION TECHNIQUES

Shaundarya Kumar[*1], Usha Rai[2] ,Rakesh singh[2], Vaibhav Prakash Srivastava[2]

[1]Kamala Nehru Institute of Technology & Management, Faridipur, Sultanpur UP, India

[2]Uttar Pradesh Technical University, India.

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***Correspondence for Author:**

*** Shaundarya Kumar**
Kamala Nehru Institute of Technology & Management, Faridipur, Sultanpur UP, India
saundarya.kumar07@gmail.com

ABSTRACT

The aim of the present study is to formulate and study of Solubility Enhancement of Dicyclomine Using Solid Dispersion Technique containing Dicyclomine in different drug to polymer ratio by Kneading Method. The cyclodextrin complexes formulated by employing 1:1 (drug: complexing agent) with kneading technique showed higher drug release.

β - CD was mixed in glass mortar along with water to obtain a homogeneous paste. The drug was then slowly added to the paste and the mixture was triturated for 1 hr. during the process the water content was empirically adjusted to maintain the consistency of the paste. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through specific sieve no. and stored in a dessicator until further evaluation.

A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug. Particles with improved wettability: The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion . Particles with higher porosity : Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier.

In order to enhance *in vitro* dissolution and content uniformity of poorly soluble drug dicyclomine by preparing solid dispersions using modified solvent fusion method, solid dispersions of drug were prepared by modified fusion solvent method using PEG 6000 and β – cyclodextrin (as carrier).

Keywords: Kneading Method; solid dispersion; Dicyclomine; inclusion complex, β – cyclodextrin, PEG 6000 physical, kneading, solvent evaporation & fusion method.

INTRODUCTION

The insufficient solubility of many new drug substances in water as well as in the aqueous gastric fluids cause problems in bioavailability. The development of solid dispersions is an appropriate means to overcome these problems and to guarantee a reasonable bioavailability. Several methods exist to prepare solid dispersions, the melting method being the most convenient. The melting procedure includes the melting of the carrier, the subsequent dissolution of the drug within the melt and finally, the cooling of the obtained solution. During the cooling process the molecular dispersion of the drug within the carrier may be maintained or the drug may recrystallize as a result of the increasing super saturation due to the lowering of temperature. Moreover, recrystallization can take place during storage as well. The precipitation usually leads to a decrease in the dissolution rate of the drug in the dissolution medium as amorphous materials dissolve faster because of their higher solubility. Therefore an attempt has been made to prevent the drug from recrystallization. (1,2)

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption . Therefore, pharmaceutical researchers' focuses on two areas for improving the oral bioavailability of drugs include:

(i) Enhancing solubility and dissolution rate of poorly soluble drugs and

(ii) Enhancing permeability of poorly permeable drugs . It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble . Unfortunately, many of these potential drugs are abandoned in the early stages of development due to the solubility problems. It is therefore important to realize the solubility problems of these drugs and methods for overcoming the solubility limitations are identified and applied commercially so that potential therapeutic benefits of these active molecules can be realized. Therefore lots of efforts have been made to increase dissolution of drug. (3,4)

Methods available to improve dissolution include salt formation, micronization and addition

of solvent or surface active agents. Solid dispersion (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method . The reasons for solid dispersion or advantages of solid dispersions are as follows: Particles with reduced particle size :Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium.

The formulation of drugs having low aqueous solubility using solid dispersion technology has been an active area of research since 1960 . Among the various approaches to improve solubility, the solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous. (5)

MATERIALS AND METHODS: Pure sample of Dicyclomine was obtained from Pfiscar India Ltd. Sonepat ,India. β-CD is purchased from SD Fine Chemicals, Polyethylene glycol (PEG6000) Sodium Lauryl Sulphate (SLS) and HCL were purchased from SD-Fine Chem.

Preparation of Physical Mixture

Physical Mixtures (PMs) of Dicyclomine with hydrophilic carriers PEG 6000 and β-CD respectively were prepared by mixing and triturating required amount of Dicyclomine and carrier for 5 min in mortar until homogenous mixture was obtained. This resulting mixture was sieved through an 80 mesh screen and stored in screw cap glass vial at room temperature. (6,7).

Solvent Evaporation Method

Dicyclomine and carrier (PEG 6000 and β-CD) in ratio of 1:1 and 1:1 respectively were dissolved in minimum volume of organic solvent (methanol) and solvent was evaporated on hot plate. The resultant solid dispersion was kept in refrigerator for about 5 min and allowed to solidify. The hardened mixtures were then powdered in mortar, sieved through an 80 mesh screen and stored in desiccator at room temperature. (8,9)

Kneading Method

β - CD was mixed in glass mortar along with water to obtain a homogeneous paste. The drug was then slowly added to the paste and the mixture was triturated for 1 hr. during the process

the water content was empirically adjusted to maintain the consistency of the paste. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through specific sieve no. and stored in a dessicator until further evaluation. (10,11)

Fusion-melt Method: The fusion-melt involves melting the compound(s) and the carrier components together at temperatures at or above the melting point of all components. In the fusion process, researchers blend the compound and carrier in a suitable mixer.

They heat, melt the blend and then cool the molten mixture rapidly to provide a congealed mass. They mill this mass to produce powders at desired particle size ranges. (12)

Experimental Methods

Spectral and absorbance measurements by using UV –Visible spectrophotometer by using,1-cm quartz cells. A simple UV spectrophotometric method was developed for the determination of Dicyclomine in pure and its pharmaceutical formulations. Dicyclomine exhibited maximum absorbance at 420 nm in Phosphate buffer (pH 7.4) Containing Sodium lauryl sulphate (0.2 %) and obeyed linearity in the concentration range of 1-10 µg/ml. (13,14,15)

Preparation of Stock Solution

Standard stock solution of Dicyclomine was prepared by dissolving 10 mg of drug in 100 ml of Phosphate buffer (pH 7.4) Containing Sodium lauryl sulphate (0.2 %) in 100 ml of volumetric flask to get a concentration of 10µg/ml. (16)

Preparation of Working Standard Solutions and construction of standard graph

To construct Beer's law plot for Dicyclomine, the stock solution was further used to prepare working standard solutions of concentrations ranging from 1 to 10 µg/ml different aliquots of working standard solutions of Dicyclomine was transferred separately into a series of 10 ml volumetric flasks and diluted to 10 ml using phosphate buffer .The absorbance were measured at λmax 296 nm against buffer as blank. The standard graph for Dicyclomine was plotted by taking concentration of drug on x-axis and absorbance on y-axis and is shown in fig 1. The drug has obeyed Beer's law in the concentration range of 1-10 µg/ml.(17,18)

Saturation Solubility Studies

To evaluate increase in solubility of Dicyclomine after formation of (SDs) or in the presence of hydrophilic carriers (PMs), saturation solubility studies were conducted. Weighed amount

of (PMs) and (SDs) were added to the 250 ml conical flask containing 100ml of distilled water. The sealed flasks were shaken by orbital shaker operating at 150 rpm at 37 ºC for 24 hours. The aliquots withdrawn were filtered through whatman filter paper and analyzed by UV spectrophotometer at 420 nm. (19,20)

Fourier-Transform Infrared Spectroscopy

The FTIR spectra were obtained by using an FTIR spectrometer – 430 (JASCO, Japan).The sample (Dicyclomine and SD) were previously ground and mixed thoroughly with potassium bromide in the ratio1:1.5 (Sample: KBr) respectively. The scanning range was 4000 to 400 cm-1**.(21)**

X-ray Diffraction

The X-ray powder diffraction patterns (XRPD) were obtained at room temperature using a Philips Analytical X-ray BV (PX1710) with cobalt as anode material and graphite monochromator, operated at a voltage of 40 kV. The samples were analyzed in the 2θ angle range of 2 ºC - 65ºC and process parameters were set as: scan step size of 0.025º (2 θ) , scan step time of 1.25s and the time of acquisition of 1hr. (22)

RESULT & DISCUSSION

Calibration Curve of Dicyclomine

Preparation of Stock Solution

100 mg of dicyclomine was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 0.1 N hydrochloric acid to get a solution of 1000 µg/ml (stock solution I). 10 ml of stock solution I was diluted to 100 ml with 0.1N HCl (Stock solution II). Further, 10 ml. of stock solution II was diluted up to 50 ml with methyl orange solution (1%w/v) and extracted with chloroform (3x15 ml). Organic layers were separated and pooled. The volume of pooled organic layer was made up to 100 ml with sodium acetate solution (Stoke solution III). This stock solution III was used to prepare a series of standard dicyclomine solutions as discussed below.

Procedure

From stock solution III aliquots of 1, 2, 3, 4, 5 6, 7 & 8 ml were transferred to a series of 10 ml volumetric flasks. The volume was made up with 0.1 N HCl to give 10, 20, 30, 40, 50, 60, 70 & 80 µg/ml of dicyclomine. The absorbance of these solutions was measured at 420

nm against blank. The same procedure was followed for the preparation of standard curve of dicyclomine in phthalate buffer pH 4.5,

phosphate buffer pH 6.8, and phosphate buffer pH 7.4. The standard curve of dicyclomine in phosphate buffer pH 6.8 with pectinex ultra-SPL was also prepared by this method, where the drug was dissolved in mixture of 99 ml of buffer and 1 ml of pectinex ultra-SPL for the preparation of stock solution III. The data are recorded in Tables 1 and the curves are plotted Figure 1

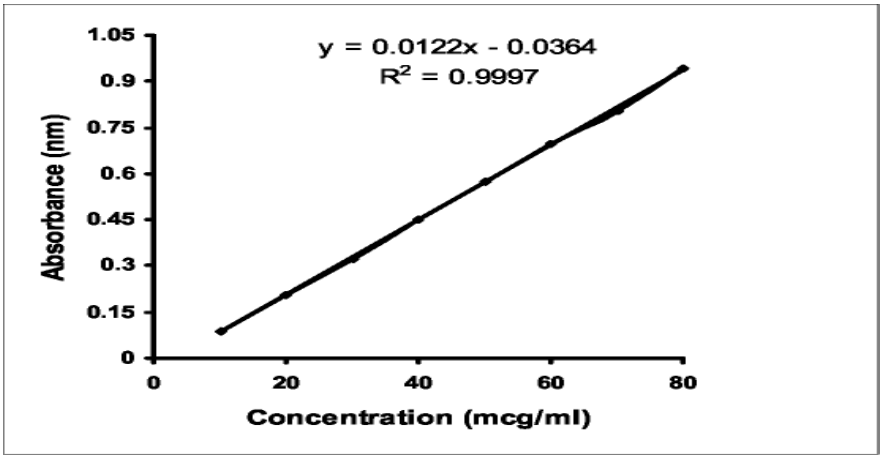

Figure 1 Calibration curve of dicyclomine in phosphate buffer pH 6.8

Tables 1

Parameters	**Values**			
	0.1 N HCl	Phthalate buffer pH 4.5	Phosphate buffer pH 6.8	Phosphate pH 7.4
ëmax (nm)	420	420	420	420
Beer's law limit (mcg/ml)	10-80	10-80	10-80	10-80
Slope (b)	0.0132	0.0161	0.0161	0.0144
Intercept (a)	0.0031	0.0201	0.016	0.0036
Regression equation (y= a+bx)	0.0123x-0.0031	0.0116x + 0.0201	0.01 1x + 0.016	0.0122x + 0.0036
Correlation coefficient	0.9991	0.9995	0.9997	0.9997

Preparation of solid complexes

Complexes of ***β***-CD with Dicyclomine were prepared in the molar ratio of 1:1 on the basis of phase solubility study by different methods like Physical mixing, Kneading, Solvent evaporation, and Fusion method.

Physical Mixture

Physical mixture was prepared by triturating Dicyclo. and β-CD together for 30 min in a clean and dry glass mortar until a homogeneous mixture was obtained. And then was forced through sieve no 100. Table-2

Kneading Method

β-CD mixed in glass mortar along with water to obtain a homogeneous paste. The drug (either in powder form or as solution with minimum quantity of methanol) was then slowly added to the paste and the mixture was triturated for 1 hr. during the process the water content was empirically adjusted to maintain the consistency of the paste. Methanol was added to assist dissolution of TEL during the process. The paste was dried at room temp., pulverized and forced through sieve no 100.5 Table-2.

Fusion Method

Dicyclo and ***β***-CD were thoroughly mixed and placed in a sealed container with a small amount of water. The contents are heated to about 1000C and then removed and dried. The mass was then pulverized and forced through sieve no 100. Table-2

Solvent evaporation Method

7,8 A solution of Dicyclomine in methanol was gradually added to equi-molar concentration of ***β***-CD in water and agitated at 500C for 30 min and toward the end of addition turbidity developed in the mixture. At the end of this period the solution was filtered, and the moist solid was kept in oven 500C for removal of last trace of solvent. The mass was then pulverized and passed through sieve no 100. Table-2

Table 2: Preparation of Dicyclomine & β-CD solid dispersions by different technique

Type of formulation	Dicyclo: :β-CD & PEG-6000 (molar ratio)	Solid dispersion Method	Media
DPPM	1:1	Physical Mixing	---------
DPKW	1:1	Kneading	Water
DPKM	1:1	Kneading	Methanol + Water
DPSE	1:1	Solvent Evaporation	Methanol + Water
DPFW	1:1	Fusion	Water

Drug Content

Samples of each solid complex were assayed for drug content by dissolving 100 mg of the complex in 100 ml ethanol. The drug content was determined at 296 nm by UV-Spectrophotometer. The experiment was conducted in triplicate.**Table-3**

Table 3. Drug content of Dicyclo. with β -CD & PEG-6000 complexes (% Drug content)

Formulation	Theoretical drug content in 100mg	Practical drug content in 100mg (mean n=3)	% Drug content
DPPM	28.74	28.02	96.68
DPKW	28.74	29.93	96.10
DPKM	28.74	28.12	96.12
DPSE	28.74	28.08	96.93
DPFU	28.74	28.11	98.08

Saturation solubility of different formulations of Telmisartan

The saturation solubility of pure Dicyclomine and its complexes with *β* -CD is shown in **Table 4**. The saturation solubility of pure **Dicyclo** is 11.9µg/ml while the saturation solubility of all other complex prepared by various methods exhibited dramatic increase in the saturation solubility. DPM and *β* -CD (complex prepared by physical mixing) showed a lower value for saturation solubility than that of other complexes, the low saturation solubility can be attributed to poor complexation efficiency during physical mixing.**Table-4 & Figure -2**

Table 4. Saturation solubility data of different formulation of Dicyclomine with β-CD & PEG-6000.

Formulation	Saturation solubility(µg/ml)
Pure Dicyclomine	12.95 ± 0.84
DPPM	78.50 ± 2.10
DPKW	132.78 ± 2.32
DPKM	141.10 ± 2.35
DPSE	119.15 ± 2.63
DPFU	122.82 ± 2.43

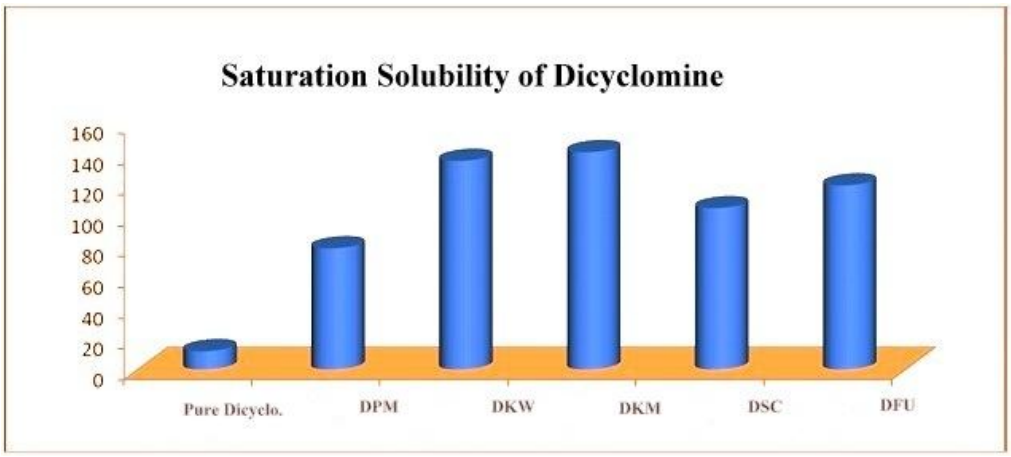

Figure 2: Saturation solubility of Dicyclomine

Fourier Transforms Infrared (FTIR) spectroscopy

FTIR of Dicyclomine pure drug are presented In **(Figure -3)** and FTIR of β – CD are presented In **(Figure -4) &**FTIR spectra of Dicyclo and β – CD its Complex are presented In **(Figure 5).** Pure Dicyclomine spectra showed sharp characteristic peaks at 3746, 2958, 1693, 1456 and 1266 cm-1 All the above characteristic peaks appears in the spectra of all Complex at same wavenumber indicating no modification or interaction between the drug and β – CD.

Powder x-ray diffractromety

Powder x-ray diffraction (XRD) of Pure Drug & β – CD with complex show in **(Figure 6&7.)** The X- ray diffractogram of Dicyclomine has sharp peak at different angle (2θ) 6.72 θ, 14.17 θ, 18.97 θ, 22.18 θ, 25.85θ show a tripical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of both physical mixtures and

solid dispersion system. Moreover, the relative intensity and 2θ angle of these peaks remains practically unchanged. Thus it can be clearly suggestive from X-ray data that there is no amorphization of Dicyclomine. and it is still in its original crystalline form.

Characterization of complexation

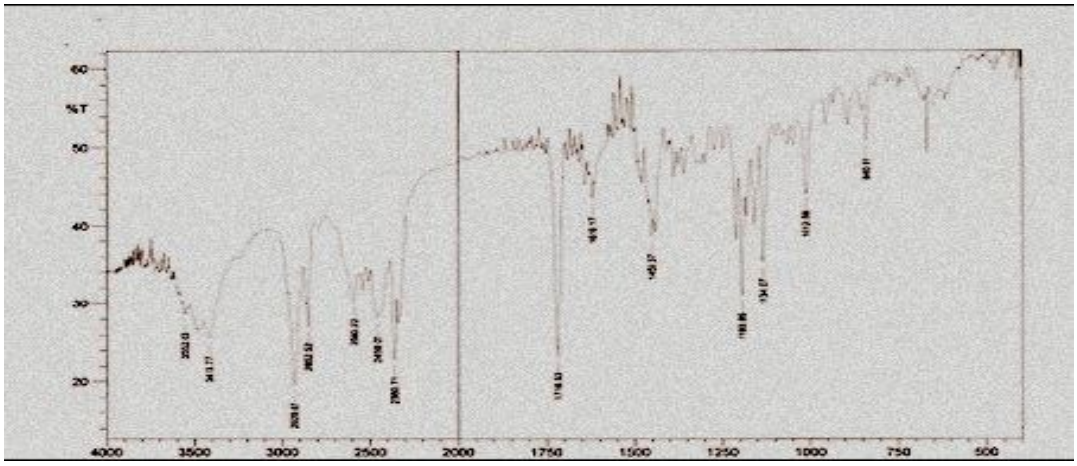

Figure 3 FTIR Spectrum of Dicyclomine

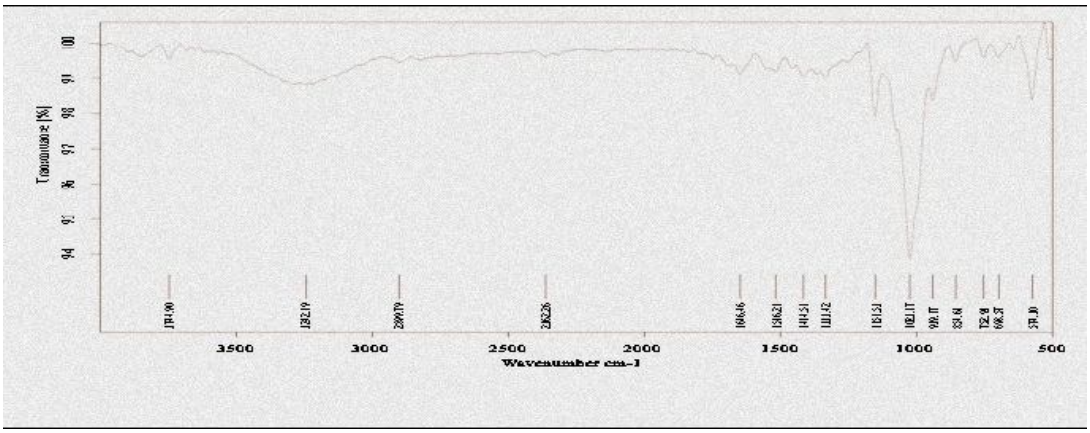

Figure 4: FTIR spectrum of pure β - cyclodextrin.

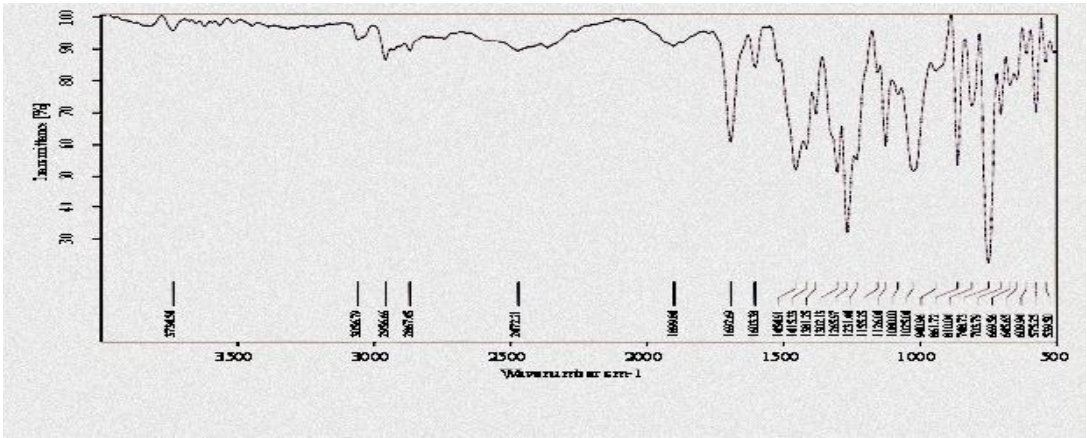

Fig. 5.FTIR spectrum of DKW (Dicyclo. with β --CD complex prepare by kneading method employing only water as solvent).

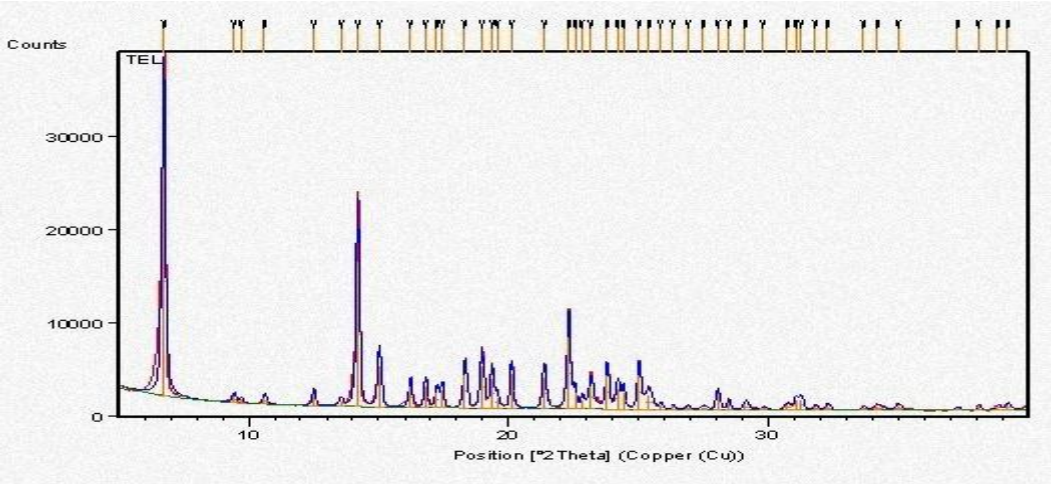

Fig.6. x-ray diffractromety of PureDicyclomine

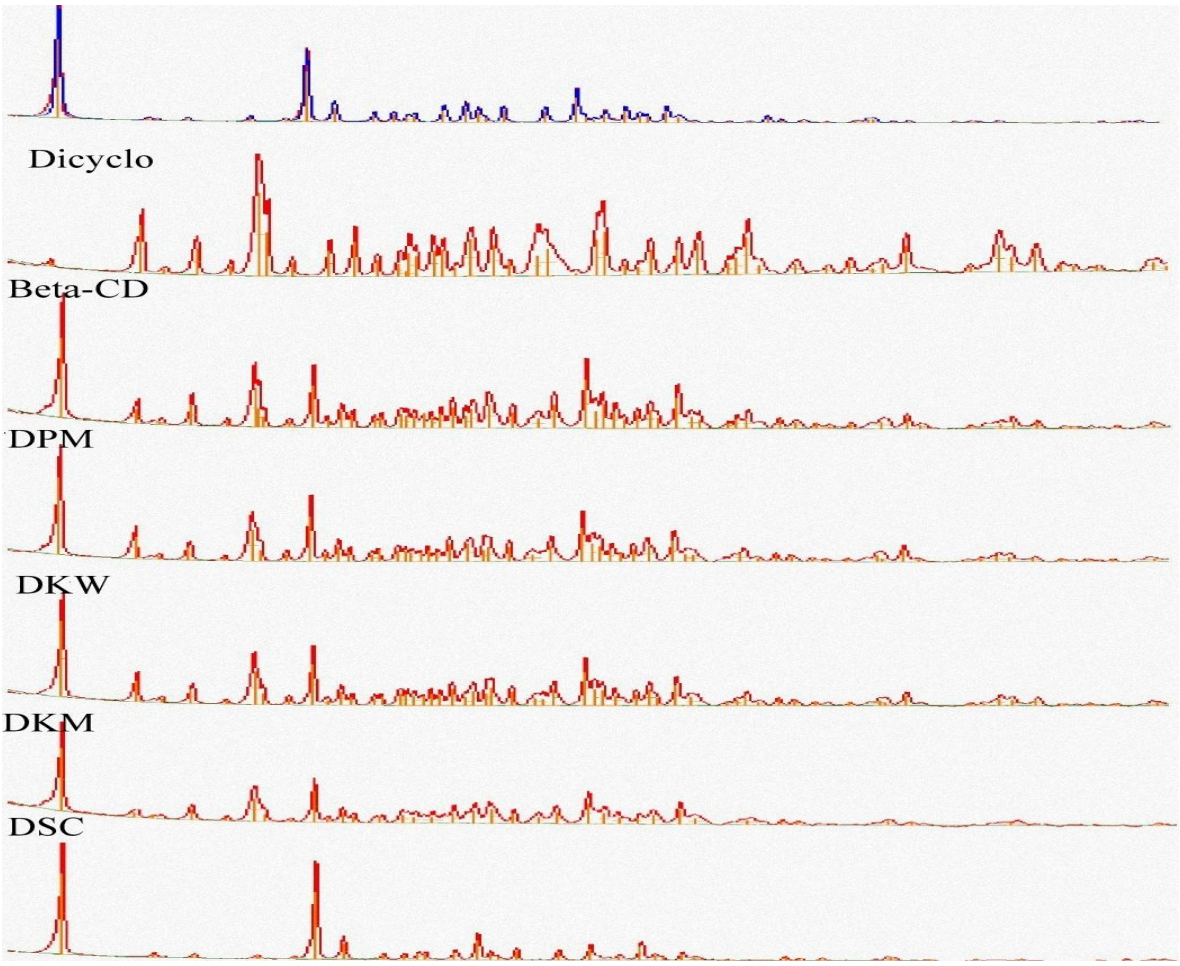

Fig 7. XRD pattern (raw data) of Dicyclomine and its various complexes with β- CD.

CONCLUSION

Solid dispersions of Dicyclomine were prepared by Different technique of solid dispersion method using carrier's β - CD. In the present work total five formulations were prepared by

using Dicyclomine with β - CD by using five convenient methods *viz,* kneading method, physical mixing method and solvent evaporation fusion method at different molar ratios of 1:1, dissolution studies were carried out in pH 7.4 phosphate buffer. The cyclodextrin complexes formulated by employing 1:1 (drug: complexing agent) with kneading technique showed higher drug release.

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REFERENCES

1. Alka Tomar , Kiran Sharma, Nitesh S Chauhan*, Ashu Mittal, Umakant Bajaj(Formulation and Evaluation of Fast Dissolving Oral Film of Dicyclomine as potential route of Buccal Delivery) Department of Pharmaceutics, KIET School of Pharmacy, Ghaziabad 2012
2. Ahire B. R., Rane B. R., Bakliwal S. R., Pawar S. P. Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Techniques Vol.2, No.3, July-Sept 2010 pp 2007-2015,
3. SP. Dhat, SA. Aphale, AP. Sherje, JA. Sakale, AV. Vaidya and SD. Vanshiv Department of Pharmaceutics, Sinhgad Institute of Pharmacy, Narhe, Pune, Maharashtra, India. Solubility Enhancement of Satranidazole Using Solid Dispersion Technique Vol. 2 (3) Jul – Sep 2011.
4. S.Muralidhar, G.Devala Rao, M.Krishna Murthy, K.Kiran Kumar,(Enhancement of dissolution rate of etoricoxib through solid dispersion technique) K.Kranthi Teja,Syed Khaja Nawaj,T.V.Narayana 10-07-2011.
5. V. Tomar1, N. Garud1, P. Kannojia1, A. Garud1, N. K. Jain2, N. Singh2. Enhancement of Solubility of Acyclovir by Solid Dispersion And Inclusion Complexation Methods 1Institute of Professional Studies, Shivpuri Link Road, Gwalior, M.P., India 2Pranav Institute of Pharmaceutical science and research, Gwalior, M.P.,- India 2010.
6. Prashant Upadhyay 1 Formulation of Fast-Release Gastroretentive Solid Dispersion of Glibenclamide with Gelucire 50/13Department of Pharmaceutics, College of Pharmacy, I.F.T.M, Delhi Road, Moradabad-244001 and Gautam Buddh Technical University, Lucknow

7. Veerendra S. Rajpurohita, Pankaj Rakhaa, Surender Goyala, Harish Durejab, Formulation and Characterization of Solid Dispersions of Glimepiride through Factorial Design Gitika Arorac and Manju Nagpald, aRajendra Institute of Technology and Sciences, Hisar Road, Sirsa-125055, India .Department of Pharmaceutical Sciences, M. D. University, Rohtak-124001, India 2011
8. Sanjoy Kumar Das1, Sudipta Roy2, Yuvaraja Kalimuthu3, Jasmina Khanam4, Arunabha Nanda5 Solid Dispersions : An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs 1&2Institute of Pharmacy, Jalpaiguri, West Bengal - 735101, India 1,3,4&5Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, West Bengal, India
9. Amir Bashiri-Shahroodi, Parya Reisi Nassab, and Piroska Szabó-Révész Preparation of a Solid Dispersion by a Dropping Method to Improve the Rate of Dissolution of Meloxicam Department of Pharmaceutical Technology, University of Szeged, Szeged, Hunga. 2008
10. Vedha Hari B.N.,Yasmin Begum A D. Department of Pharmaceutical Technology Solid dispersions, Carrageenan, Hot stage microscopy, HIV, Anti-retroviral Therapy (ART) 30 July2010, Revised and Accepted: 05 Oct 2010
11. Drug profile, Dicyclomine HCl, http://www.drugs.com/cdi/dicyclomine hydrochloride.html. As accessed on June 14,2012.
12. Drug bank, Drug profile, Dicyclomine HCl, http://drugbank.ca/drugs/DB00863(APRD 00113). As accessed on February 14,2012.
13. Monograph of Dicyclomine Hydrochloride-Dicyclomine Hydrochloride tablet cardinal health: 592. As accessed on June 5,2012
14. Sekikawa, H., Fukyda, W., Takada, M., Ohtani, K., Arita, T., & Nakano, M.(1983). Dissolution behavior and gastrointestinal absorption of dicumarol from solid dispersion-systems of dicmarol-polyvinylpyrrolidone and dicumarol- beta-cyclodextrin. *Chem. Pharm. Bull., 31,* 1350–1356.
15. Serajuddin, A. T. M., Sheen, P. C., Mufson, D., Bernstein, D. F., & Augustine, M. A. (1988). Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci., 77,* 414–417.
16. Tachibana, T., & Nakamura, A. (1965). A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers–dispersion of beta-carotene by polyvinylpyrrolidone. *Kolloid-Z Polym., 203,* 130–133.

17. Takayama, K., Nambu, N., & Nagai, T. (1982). Pharmaceutical interactions indosage forms and processing. 28. Factors affecting the dissolution of ketoprofen from solid dispersions in various water-soluble polymers. *Chem. Pharm. Bull., 30*, 3013–3016.
18. Tauler, R. (1995). Multivariate curve resolution applied to second order data. *Chemom. Intell. Lab. Syst., 30*, 133–146.
19. Tauler, R. (2001). Calculation of maximum and minimum band boundaries of feasible solutions for species profiles obtained by multivariate curve resolution. *J. Chemom., 15*, 627–646.
20. Tauler, R., Casassas, E., & Izquierdo-Ridorsa, A. (1991). Self-modeling curveresolution in studies of spectrometric titrations of multi-equilibria systems by factor-analysis. *Anal. Chim. Acta, 248*, 447–458.
21. Tauler, R., Smilde, A., & Kowalski, B. R. (1995). Selectivity, local rank, 3- way data-analysis and ambiguity in multivariate curve resolution. *J. Chemom., 9*, 31–58.
22. Van Benthem, M. H., Keenan, M. R., & Haaland, D. M. (2002). Application of equality constraints on variables during alternating least squares procedures. *J. Chemom, 16*, 613–622.