

## RESEARCH AND DEVELOPMENT OF DIAZEPAM SOLID DISPERSION POWDER USING NATURAL POLYMERS

UDITI HANDA<sup>1</sup>, KAMAL SAROHA<sup>2</sup>

<sup>1</sup>Guru Gobind Singh College of Pharmacy, Yamuna Nagar 135001, Haryana, India, <sup>2</sup>Department of Pharmaceutical Sciences, Institute of Kurukshetra University, Kurukshetra 136119, India  
Email: uditipharmacist@gmail.com

Received: 15 Jun 2018, Revised and Accepted: 03 Aug 2018

### ABSTRACT

**Objective:** The objective of this study was to enhance the solubility and dissolution rate of a poorly water-soluble drug by solid dispersion (SD) technique, in order to conduct an investigation of the effect of these natural hydrophilic polymers on release mechanism from SD.

**Methods:** The SD of diazepam (DZM) were prepared by using modified sodium alginate (SA) and modified guar gum (GG) in different drug: polymer ratios (1:1 and 1:2) by using physical mixture method (PM) and fusion method (FM). Further, the formulations were characterized for calibration curve, Fourier transforms infrared spectroscopy (FTIR) studies, % age practical yield, drug content estimation, solubility studies, dissolution studies.

**Results:** The pure drug and SD were characterized by pre and post-formulations studies. The %age practical yield ranged from 92.9±0.25 to 49±0.57%, and the drug content estimation ranged from 99.34±0.40 to 65.25±0.25 %. The FTIR studies shown that the compatibility between pure drug and natural polymers was stable. All the SD showed improved solubility as compared to the pure drug (PD). SD prepared with modified SA (1:2) by PM and FM shown the huge enhancement of solubility and dissolution rate of the DZM. This can be specific to the improvement in wettability and dispersibility, as well as enhances the drug amorphous fraction.

**Conclusion:** On the basis of the research study, the SD technique shows the enhancement in the solubility of poorly water-soluble drug using natural polymers. SD containing natural polymers prepared with PM and FM shown the remarkable improvement in the release outline compared with PD, DZM.

**Keywords:** Diazepam, Solid dispersions, Natural polymers, FTIR, Methods

© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)  
DOI: <http://dx.doi.org/10.22159/ijap.2018v10i5.27975>

### INTRODUCTION

To improve the therapeutic efficacy of poorly water-soluble drugs through oral administration, which often shows the poor bioavailability due to their slow and irregular levels of the absorption at the site of therapeutic action. Drugs suffered from dissolution rate limited G. I. T absorption generally shows a reduction in particle size of the formulation due to the increase in the surface area which automatically improves the dissolution and bioavailability. However, micronizing of the drugs leads to the formation of a bunch of particle in cluster form, which results in poor wettability of the drug. To overcome these problems, SD of poorly water-soluble drug with water-soluble polymers is prepared to enhance the solubility as well as dissolution profiles [1-3].

DZM, as the most representative benzodiazepine, is widely used as anticonvulsant, anxiolytic, sedative agent, hypnotic, muscle relaxant and is also very useful in suppressing febrile and epileptic convulsions [4, 5]. It is used in alcohol withdrawal symptoms, or muscle spasms and sometimes it is used to treat seizures with other medications [6-8]. As benzodiazepines, DZM is a positive allosteric modulator of the Gamma-aminobutyric acid type A receptors (GABAA). The binding of DZM to the GABAA receptor increases the affinity of the receptor, thereby increasing the opening frequency of GABAA receptor, resulting in an increased influx of Cl<sup>-</sup> ion into neurons which prevents the further excitation of the cell. The excitability of the neurons is therefore diminished [4, 6, 7, 9].

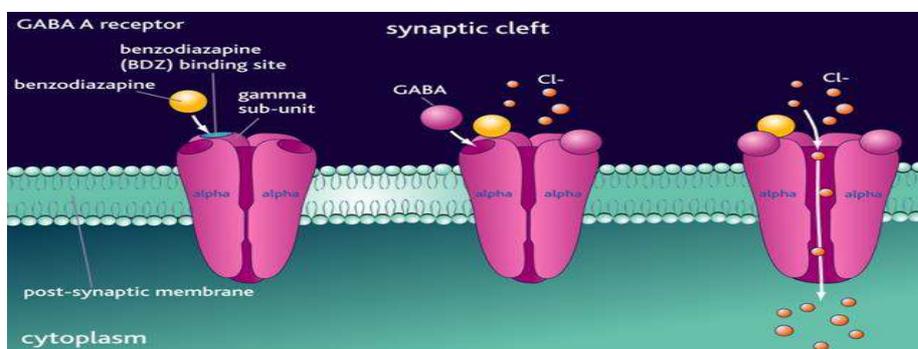


Fig. 1: Schematic representation of the mode of action of DZM [10]

Although parenteral therapy is the most faster way to get a rapid action, this drug administration route shows some difficulty to the patient, such as the pain, needle fear, the syringe manager, the risk of

needle infection, etc., carrying disconcert and poor patient compliance. Oral immediate-release dosage forms can be a good alternative to intravenous therapy. However, DZM when

administered orally due to the poor aqueous solubility, it produces erratic and delayed absorption. [11-16]. The enhancement in the solubility and/or dissolution rate/bioavailability of DZM may arrive from the preparation of SD [5, 7, 9]. The increase in solubility/dissolution rate from the SD can be attributed by the merging of following different factors; particle size reduction of drug, solubilising effect on the drug by the water-soluble polymers due to improved wettability and dispersibility of the drug particles by using various hydrophilic polymers and the possible formation of a accessible dispersion that has a higher solubility resulting in rapid dissolution rate. Drug release from solid dispersions is described in several ways. Immediate release drug products allow drugs to dissolve with no intention of delaying or prolonging the dissolution or absorption of the drug [7, 9].

Natural polymers were used in this research article first was SA: Due to the inherent mucoadhesive nature of alginate, it is expected that these SDs would be retained over a longer time-period in the stomach, which is the predominant absorption site of DZM, thus further extending their utility. There is an urgent need for the development of more such eco-friendly technologies keeping in view

the stringent environmental regulations [17-21]. And second was GG: It is a water-soluble fibre, act as a bulk-forming laxative and is effective in promoting regular bowel movements and relieving constipation. Due to the swelling nature of the carrier, the extensive surface of the carrier is increased during dissolution, and the dissolution rate of the deposited drug is markedly enhanced. Water retention capacity of the carrier is the amount of water retained in it that indicates the ability of carrier towards hydrophilic nature. When a drug-carrier particle comes in contact with the dissolution fluid, seeping of dissolution media into the drug-polymer particle takes place, which initiates the formation of a stagnant gel layer of polymer around the particle [22-25]. The main aim of this study was to improve the solubility and dissolution rate of DZM by using natural polymers with SD technique.

## MATERIALS AND METHODS

### Materials

The sample of DZM was gifted from Symbiosis P'ceutical Pvt. Ltd. Kalaamb Himachal Pradesh (H. P). SA and GG was gifted by Loba Chemie Pvt. Ltd. Mumbai.

Table 1: List of materials used

Category	Material	Supplier
Drug	Diazepam	Symbiosis P'ceutical Pvt. Ltd. Kala aam (H. P)
Polymer	Sodium alginate	Loba chemie pvt. ltd. Mumbai.
Polymer	Guar gum	Loba chemie pvt. ltd. Mumbai.
Solvent	Methanol	HiMedia Laboratories Pvt. Ltd., Mumbai.

### Preparation of DZM SD

#### Physical mixing method

In this process, 50 mg of DZM was weighed accurately, and physical mixtures were formulated by the mixing of drug and polymer in geometric proportions using the mortar pestle. The resultant SD was passed through a No.60-mesh sieved, stored in dessicator or airtight container until used for further studies [16, 20, 21, 26].

#### Fusion method

Melted the polymer (molten state) and then incorporate the drug, melted mixture was cooled and solidified rapidly in an ice bath under vigorous stirring. The final mass was crushed, pulverized and sieved by 44-mesh sieve [2, 3, 16, 20, 21, 26].

### Characterization of SD

#### Calibration curve of DZM

##### In methanol

10 mg DZM was weighed accurately and dissolved in 100 ml of methanol to produce a 0.1 mg/ml solution. 20 ml of the above

solution was transferred in a volumetric flask and volume was made up to 100 ml with the distilled water. 1, 2, 3, , up to 10 ml of this solution was taken in the 10 ml of volumetric flasks and the distilled water was added up to the mark to prepared the standard solutions. These serial dilutions were carried out from the stock solution to get different DZM concentrations. Standard solutions were then analyzed by the UV spectrophotometer at 230 nm and the absorbance was to be noted. Then the graph was plotted against the absorbance values v/s drug concentration and Diazepam standard curve was produced [7, 9, 12, 13, 16, 20].

##### In PBS (pH6.8)

Weighed accurately diazepam amount was dissolved in the 5 ml methanol and diluted to the 100 ml with the poshate buffer solution (PBS). Diluted five the above drug solution to get a stock solution having a concentration (25 µg/ml). Fractional of this stock solution was further diluted to 25 ml with the buffer solution having the concentrations from 1-9 µg/ml to get the standard solutions. The above solutions were scanned from 200 to 400 nm against a blank (PBS). Standard solutions were set to prepared three times a day from the same stock solution (25 µg/ml) and afterward, solution was scanned to get the absorbance value (A) at 2-nm interval [9, 13, 16].

Table 2: Composition of solid dispersions formulation

Method	Carrier	Drug: carrier ratio	Batch code
PM	GG	1:1	F1
		1:2	F2
	SA	1:1	F3
		1:2	F4
FM	GG	1:1	F5
		1:2	F6
	SA	1:1	F7
		1:2	F8

### FTIR spectroscopy

The FTIR spectral of the drug and solid dispersion in different ratios were recorded with FTIR spectrophotometer. The sample was prepared by mixing with KBr then compressed into disks by a hydraulic press. The disks were loaded into FTIR holder and scanned for absorbance at 4000-400 cm<sup>-1</sup> [8].

### % age practical yield

For the determination of the efficiency of any method of production, % age practical yield was calculated. SD was collected and weighed to calculate the practical yield (PY) from the following equation: [2, 3, 16, 20]

$$PY (\%) = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoretical mass (drug+carrier)}} \times 100$$

### Drug content estimation

Dissolved the accurately weighed quantity of SD equivalent to 10 mg in 10 ml of methanol solvent. Further, 1 ml of solution was taken and diluted suitably. The solution was then filtered through whatman filter paper. The determination of DZM content was carried out at 240 nm by UV-visible spectrophotometer. The % age drug content was to be calculated using the following equation: [16, 20, 21, 26]

$$\text{Drug content (\%)} = \frac{\text{Actual amount of the drug in Solid dispersion}}{\text{Theoretical amount of the drug in Solid dispersion}} * 100$$

### Solubility studies

The flasks containing 10 ml of PBS (6.8 pH) and distilled water and dissolve the PD and SD in excess quantity in it. The samples were placed in a magnetic stirrer at 37 °C for 1 h. The solutions were analyzed by the UV-spectrophotometer [20, 21, 26].

### Dissolution studies

The *in vitro* dissolution study was carried out in a paddle type Dissolution Apparatus (USP Type II). The SD containing 40 mg

equivalent DZM (fixed amount) from each formulation was calculated for dissolution profile. PBS (pH 6.8) with 900 ml volume was used as dissolution medium, in each dissolution sink at 37 °C temperature and 100 rpm paddle speed. The dissolution was conducted for 1 h and withdrawn the 5 ml sample at predetermined intervals of 5, 10, 20, 30, 40, 50 and 60 min. Each and every time compensated by another fresh 5 ml buffer solution with the 5 ml withdrawn sample. Then filtered and withdrawn dissolution sample through Whatman No.41 filter paper in a test tube. The absorbance was to be noted by scanning the dissolution samples by the UV-VIS spectrophotometer at 240 nm [2, 3, 16, 20, 21, 26].

## RESULTS

### DZM calibration curve

The calibration curve of DZM was prepared in methanol and phosphate buffer (pH6.8) solution at 240 nm, and the absorbance values at different concentrations of DZM in methanol sol<sup>n</sup> are shown in fig. 2. Values of R<sup>2</sup> (regression coefficient) were found to be 0.996 and 0.940.

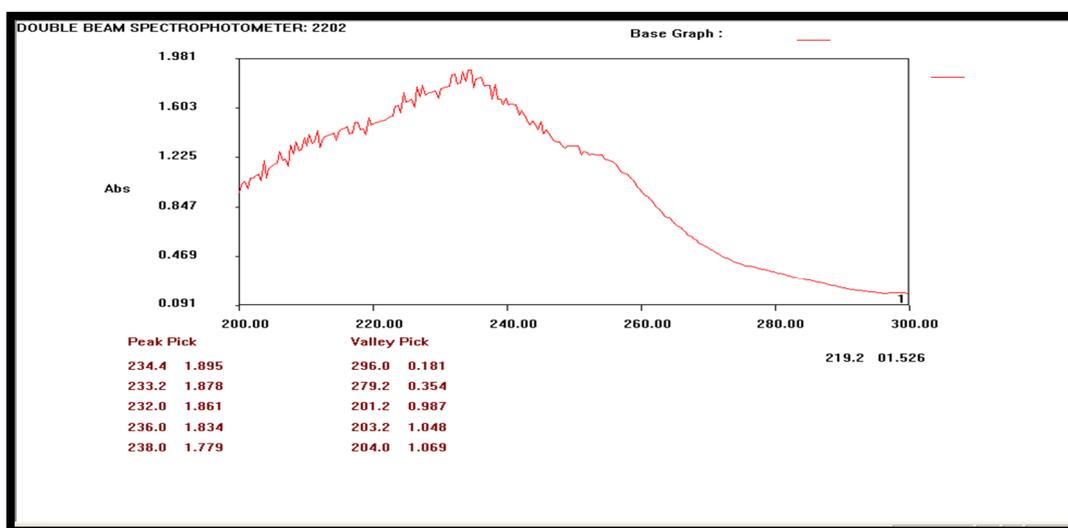


Fig. 2:  $\lambda_{\text{max}}$  scan for DZM

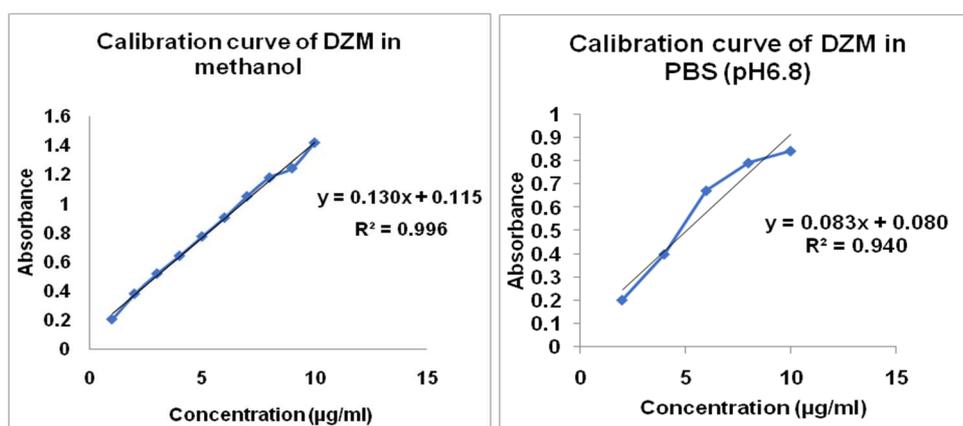


Fig. 3: Calibration curve of DZM

### Percentage practical yield and drug content

Percentage practical yield of DZM SD was in the range of 92.9±0.25 to 49±0.57%. The % age yield was low for 1:1 of sodium alginate by fusion method and high for 1:1 of GG by PM. DZM content range of 99.34±0.40 to 65.25±0.25 % was to be found. The drug content was

low for 1:1 of by fusion method and high for 1:1 of sodium alginate by physical mixing method.

### FT-IR studies (Drug-excipients compatibility studies)

There was no interaction between the DZM, GG, SA and the DZM SD formulations were shown in the FT-IR spectra (fig. 4-7).

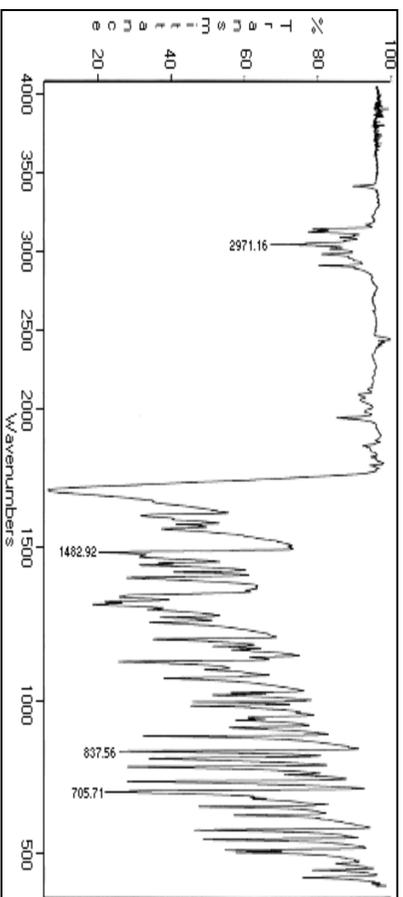


Fig. 4: FT-IR spectra of diazepam (DZM)

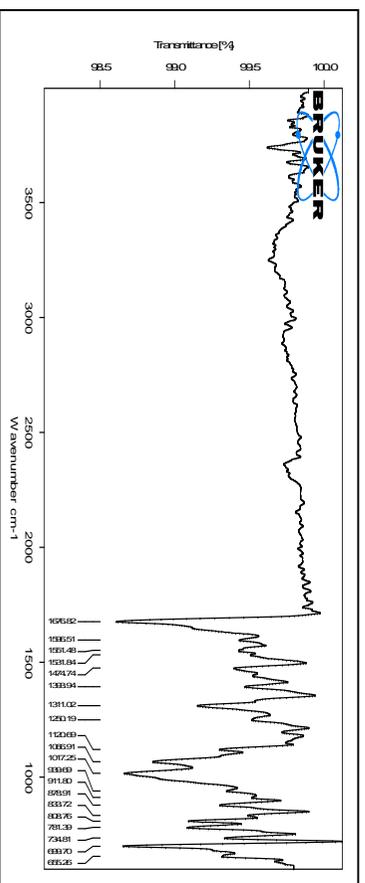


Fig. 5: FT-IR spectra of DZM and guar gum (GG)

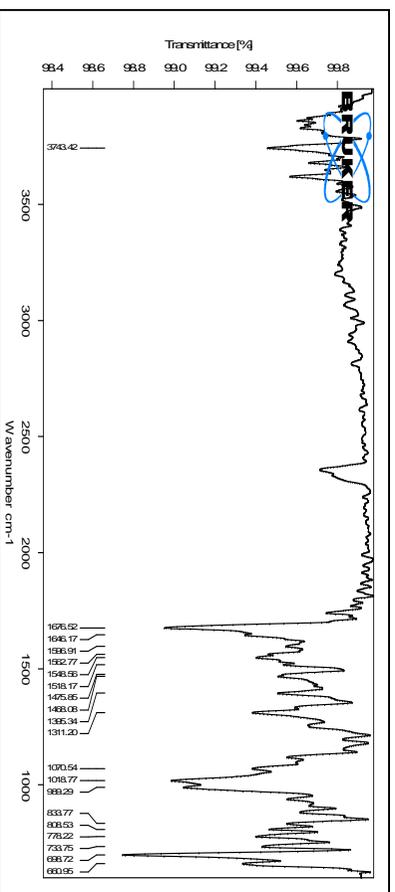


Fig. 6: FT-IR spectra of DZM and sodium alginate (SA)

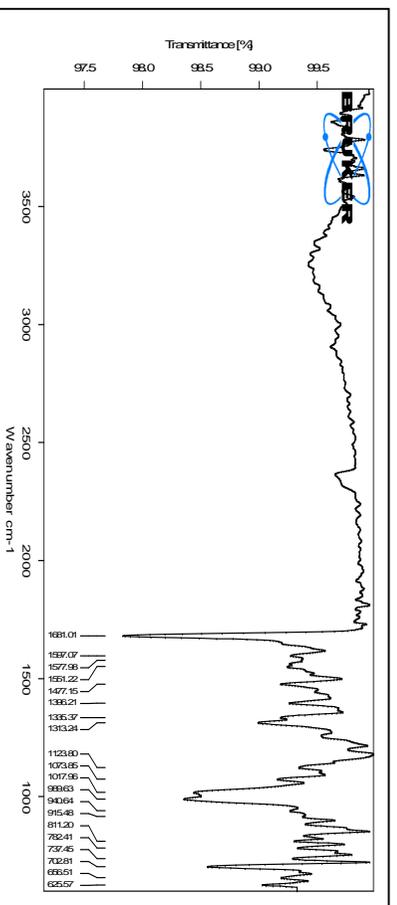


Fig. 7: FT-IR spectra of solid dispersions (SD)

Table 3: Solubility of PD and formulations F1 to F8 in distilled water and PBS pH 6.8

Formulation batches	Solubility analysis (mg/ml)	
	(Distilled water)	(PBS) (pH 6.8)
Pure drug	0.02±.006	0.0623±.0001
F1	0.08±.005	0.116±.0009
F2	0.0755±.005	0.115±.0008
F3	0.116±.0004	0.107±.0006
F4	0.125±.004	0.106±.001
F5	0.116±.0004	0.103±.0006
F6	0.067±.0004	0.076±.0006
F7	0.115±.0006	0.106±.0005
F8	0.106±.001	0.128±.006

mean±Standard deviation, n = 6

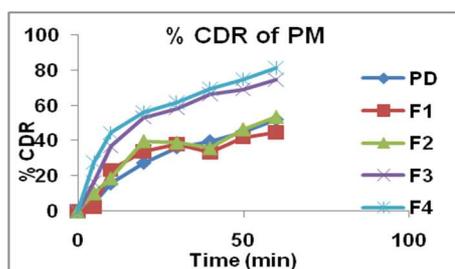
### Solubility analysis

The DZM solubility in PBS with modified SA (1:2) by FM was found to be 0.128±.006 mg/ml.

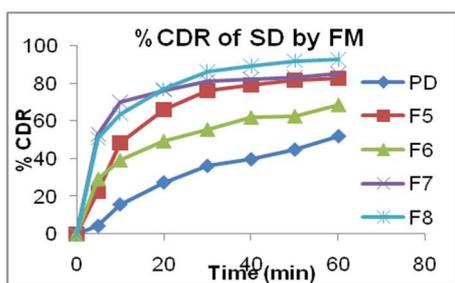
### In vitro dissolution profile

In 0.2 M phosphate buffer the *in vitro* dissolution study of PD and all the formulations was to be carried out. Dissolution profile for various batches of SD (F1 to F8) in PBS (pH 6.8) is given in fig. 8. The dissolution curve of DZM, by PM and FM are shown in above figures, from these it was concluded that the enhancement of the dissolution rate of DZM to a greater level by FM.

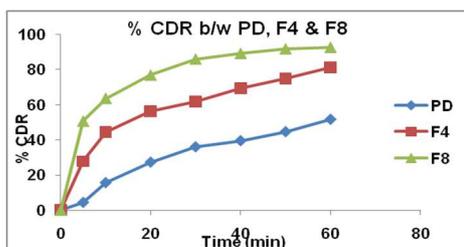
In case of PD only 51.51±0.32% was dissolved at the end of 1hr in PBS (pH 6.8), SDs by PM show a release rate up to 81.58±0.23% and SDs by FM show a release rate up to 92.8±0.21% as we can see the graphical representation in fig. 8.



(A)



(B)



(C)

Fig. 8: (A) dissolution data of PD and DZM SD by PM (F1-F4), (B) dissolution data of PD and DZM SD by FM (F5-F8), (C) dissolution data of PD and SDs of optimized formulations batch F4 and F8

### DISCUSSION

From the above observation, it was concluded that the DZM solubility was increased as a linear function of carrier concentration. All the SD showed enhanced solubility as compared to PD as shown in table 3. The observation indicated that due to the presence of the drug in the amorphous state increased the dissolution rate of DZM SD (F8) as compare to SD by PM and PD. Compared with the PD, PM, FM, the dissolution was found to increase in the following order.

### Pure drug<physical mixture<fusion method

The result of these dissolution data of SD by PM and FM shown the enhancement of dissolution profile as compare to PD as shown in fig.8 (C). The presence of natural polymer might increase the wettability and dissolution rate of the drug (DZM). As far as FTIR interpretation shows three signals at 3000 nm, 1442 nm and 837.56 nm was due to the-CH<sub>2</sub>-CCH (blend) and-NCO (blend) groups of the PD in fig. 4 but the spectra shown in the fig. 5 to 7 shown no signal at 3000 nm, 1442 nm and 837.56 nm which results in no interaction b/w the PD, SA, GG, SD. The evaluated data of this research work shows the improvement in the solubility, dissolution rate and also the bioavailability which was arrived from the preparation of SD. However, DZM when administrated orally due to the poor aqueous solubility, it produces erratic and delayed absorption. The study was to done to overcome these problems so that the oral pharmaceutical formulation was a good alternative to intravenous therapy.

### CONCLUSION

From the above evaluation, it was inter-puted that the DZM dispersions formulated by SD technique shows the enhancement in the solubility of poorly water-soluble drug using natural polymers. FM contains the modified SA (1:2) was used to prepared SD and was the best method which improves the drug dissolution as compare to PM containing modified GG or PD. The presence work unveil that optimum level of natural hydrophilic polymers ensure rapid absorption of drug (DZM) and this was achieved by SD technique. From the evaluated data, it was concluded that the natural polymer and the ratio of drug-polymer show the enhancement in the solubility, dissolution rate as well as bioavailability of the drug (DZM) by SD technique.

### LIST OF ABBREVIATIONS

DZM = Diazepam, PM = Physical mixing method, FM = Fusion method, GG = Guar gum, SA = Sodium alginate, SD = Solid dispersions, PD = Pure drug, PBS = Phosphate buffer solution, PY = Practical yield, pH = Negative logarithm of hydrogen ion concentration, BCS = Biopharmaceutical Classification System, GIT = Gastrointestinal tract, FTIR = Fourier transform infra-red spectroscopy, GABA = Gamma-aminobutyric acid

### ACKNOWLEDGEMENT

The authors would like to thanks to Symbiosis P'ceutical Pvt. Ltd. Kala amb (H. P).

### AUTHORS CONTRIBUTIONS

All the author have contributed equally

### CONFLICT OF INTERESTS

The authors declare no conflict of interest to this research article

## REFERENCES

- Chowdary KPR, Sankar Ravi K. Recent research on solid dispersions employing superdisintegrants and surfactants as a carrier. *Int J Chem Sci Technol* 2015;378-86.
- Singh S, Yadav L. A review on solid dispersion. *Int J Pharm Life Sci* 2011;2:1078-95.
- Kapoor B, Kaur R. Solid dispersion: an evolutionary approach for solubility enhancement of poorly water-soluble drugs. *Int J Recent Adv Pharm Res* 2012;2:1-6.
- Tripathi KD. *Essential of medical pharmacology*. 7<sup>th</sup>ed. Jaypee brothers medical Publication; 2013. p. 372-11.
- Shah SN. Development and validation of simple uv-spectrophotometric Method for quantitation of diazepam in api and solid dosage formulation. *World J Pharm Med Res* 2015;2:1-4.
- Ada K. Properties of Diazepam (valium); 2007. p. 1-2.
- Hadziabdic J, Elezovic A, Hadzovic S, Vehabovic M. The solubility-intrinsic dissolution rate of diazepam and inclusion complexes diazepam with 2 hydroxypropyl- $\beta$ -cyclodextrin. *Int J Sci Technol Soc* 2013;24-35. Doi:10.11648/j.ijsts.20130101.14
- Patel SA. Simultaneous spectrophotometric determination of diazepam and propranolol hydrochloride in tablets. *Curr Res Pharm Sci* 2011;1:25-30.
- Daharwal SJ. Development and validation of UV spectrophotometric method for simultaneous estimation of diazepam and propranolol in bulk drug and its formulations. *Asian J Pharm Anal* 2013;3:20-3.
- thefisheriesblog.com [Last accessed on 15 May 2018]
- Josep ER. Use of micellar mobile phases for the chromatographic determination of clorazepate, diazepam, and diltiazem in pharmaceuticals. *J Chromatographic Sci* 2000;30:521-7.
- IP. *Indian Pharmacopoeia commission*. Ghaziabad 2007;2:1013-4.
- Nebojsa D Cekic, Sanela M Đorđević, Sasa R Savic. A full factorial design in the formulation of diazepam parenteral nanoemulsions: physicochemical characterization and stability evaluation. *Adv Technol* 2015;69-77. Doi:10.5937/savteh1501069C
- Manogar PG, Hari BNV, Devi DR. Emerging liquid compact technology for solubility enhancement of BCS class-II sDrug. *J Pharm Sci Res* 2011;3:1604-11.
- Sylaja B, Srinivasan S. Experimental and theoretical investigation of spectroscopic properties of diazepam. *Int J ChemTech Res* 2012;4:361-76.
- Alway B, Sangchantra R, Stewart PJ. Modeling the dissolution of diazepam in interactive lactose mixtures. *Int J Pharm* 1996;130:213-24.
- Shanmugam. Natural polymers and their applications. *Int J Pharm Sci Rev Res* 2005;37:478-81.
- Singh Anupama. Release behavior of drugs from various natural gums and polymers. *Polim Med* 2011;41:73-80.
- FMC biopolymer. Alginate. *Nova Matrix Ultrapure Biopolymer Systems*; 2011. p. 1-2.
- Howlader Md, Chakrabarty JK, Faisal KS. Enhancing dissolution profile of diazepam using hydrophilic polymers by solid dispersion technique. *Int Curr Pharm J* 2012;1:423-30.
- Kaza R, Kumar AG, Charan YR. A study on the dissolution enhancement of gliclazide using natural polymers. *Int J Innovative Pharm Res* 2012;3:194-8.
- Gupta A, Verma DK. Guar gum and their derivatives: a research profile. *Int J Adv Res* 2014;41:680-90.
- Prasad SS, Rao KM. Synthesis and characterization of guar gum-g-Poly (Acrylamidoglycolic acid) by redox initiator. *Indian J Adv Chem Sci* 2012;1:28-32.
- Tripathi S, Das MK. Guar gum: present status and applications. *J Pharm Sci Innovation* 2013;2:24-8.
- Shejul A, Deshmane S, Biyani K. Modified natural carrier in solid dispersion for enhancement of solubility of poorly water-soluble drugs. *J Drug Delivery Ther* 2014;4:111-6.
- Kaza R, Raju YP. Dissolution enhancement of valsartan using natural polymers by solid dispersion technique. *Scholars Res Library De Pharm Lett* 2013;5:126-34.