WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 1, 1449-1457. Research Article ISSN 2277– 7105

BIOAVAIABILTY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG USING DIFFERENT METHODS

Sruthy S. Nair*[1], Anuroop U. P.[1] and Ajith Babu T. K.[2]

[1]Department of Pharmaceutics, Malik Deenar College of Pharmacy, Seethangoli, Bela Post, Kasaragod.

[2]Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Seethangoli, Bela Post, Kasaragod.

Article Received on
10 November 2021,

Revised on 01 Dec. 2021,
Accepted on 22 Dec. 2021

DOI: 10.20959/wjpr20221-22718

***Corresponding Author**
Sruthy S. Nair
Department of Pharmaceutics, Malik Deenar College of Pharmacy, Seethangoli, Bela Post, Kasaragod.

ABSTRACT

Study was mainly designed to solve the drawbacks of low bioavailability of poorly soluble drug by preparing solid dispersion. Drug - solid dispersion was developed by melt solvent method kneading method, and co-precipitation method to modify the release and enhance solubility of the drug. The physical state of the dispersed carvedilol in the polymer matrix was characterized by Fourier-transform infrared spectroscopy, super saturation solubility testing and dissolution studies. The present study indicated that the use of various solid dispersion methods by using water soluble carriers improved the solubility of poorly water soluble drug.

KEYWORDS: Solubility & Bioavailability enhancement, Carvedilol, Solid dispersion.

INTRODUCTION

A solid dosage form is a drug delivery system that includes tablets, capsules, sachets, and pills, as well as bulk or unit-dose powders and granules. Among them, tablets and capsules are most frequently given by this route. From a patient's perspective, swallowing a dosage form is far more comfortable and a familiar means of taking medication than getting injected.

Oral drug administration still continues to be the most preferred route of drug delivery due to its manifold advantages including non- invasiveness, versatility and most important patient compliance. The long and continuing history of the development of new technologies for

administration of drugs, the tablet form remains the most commonly used dosage form due to ease of production, being inexpensive and patient friendly.[1]

Low water solubility tends to the limited bioavailability and absorption of these agents. The developments of a suitable oral formulation for some drugs always have problems, which have very low water solubility. The process of solubilisation involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.[2]

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problem associated with these orally administered drugs was their low solubility in biological fluids, which resulted into poor bioavailability after oral administration.[3] Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Is a well-known approach for improvement of the dissolution rate and bioavailability of drugs that are poorly water soluble.

The carriers used have to be physiologically inert compounds that are readily water-soluble or water insoluble for fast or controlled dissolution respectively. To achieve faster dissolution rate of poorly water-soluble drug, the drug is dispersed at molecular level in a rapidly water-soluble inert carrier to form a solid dispersion. Successful dispersion of the drug in the carrier, at molecular level, leads to formation of homogeneous phase of the solid dispersion. When such a product comes in contact with gastric fluid, then the water-soluble carrier rapidly dissolves leading to immediate release of the drug at the desired molecular level to cause dissolution with consequent improvement of bioavailability.[4,5]

METERIALS AND METHODS

Materials

The following materials were used: Carvedilol (Shasun Pharma, Pondichery), PVPK30, β-cyclodextrin, talc, magnesium stearate (Chemdyes Corporation, Rajkot), Methanol (Nice Chemicals Pvt. Ltd, Cochin), PEG6000, HPMC K100M, lactose, cross carmalose sodium (Yarrow Chem Pvt. Ltd, Mumbai).

Methods

Preformulation Studies

Preformulation study is the first step in rational development of a dosage form. It can be defined as an investigation of physical and chemical properties of a drug substance alone and also when combined with excipients. Preformulation studies were performed on the drug, which included solubility, melting point determination and compatibility studies.

Preparation of Solid Dispersion

Melt Solvent Method

Solid dispersion of carvedilol-PVPK30 was prepared by melt solvent method. Accurately weighed drug was dissolved in organic solvent and the solution was incorporated in to the melt of carrier by pouring in to it. It was cooled suddenly. The mass was kept in desicator for complete drying. The solidified mass was crushed, pulverized and passed through specific sieve and stored in a desicator until further evaluation.[6]

Kneading Method

Solid dispersion of carvedilol-PEG6000 and carvedilol-HPMC K100M were prepared by kneading method. Polymer was mixed in glass mortar along with solvent to obtain a homogenous paste.

The drug was then slowly added to the paste and the mixture was triturated for 1 h. During the process the water content was empirically adjusted to maintain the consistency of paste. The paste formed was dried under vacuum for 24 h. Dried powder was passed through specific sieve and stored in a desiccator until further evaluation.[7,8]

Co-Precipitation Method

Solid dispersion of carvedilol-betacyclodextrin was prepared by co-precipitation method. Accurately weighed carrier was dissolved in water and drug in organic solvent. After complete dissolution the aqueous solution of carrier was poured in to the organic solution of the drug. The solvents were then heated and evaporated. The dispersion was pulverized with pestle and motor, sieved and dried.[9]

Evaluation of Solid Dispersion

Solid dispersions were evaluated and characterized by the following methods.

Percentage Practical Yield

Percentage practical yield was calculated to know the percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. CD complexes were collected and weighed to determine practical yield from the following equation:

$$\%\ Practical\ yield = \frac{Therotical\ mass\ (Drug + Carrier)}{Practical\ mass\ solid\ dispersion} \times 100$$

Drug Content

100 mg of solid dispersion was taken in a 50 ml volumetric flask and dissolved in 40 ml methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted and assayed for drug content using UV spectrophotometric method at 2 nm.

Saturation Solubility Study

To evaluate increase in solubility of carvedilol after solid dispersion formulation saturation solubility measurements were carried out as follows: Known excess of solid dispersion formulation was added to 10 ml of distilled water. Samples were shaken for 24 h at room temperature in a rotary flask shaker. Samples were then filtered suitably diluted and analysed spectrophotometrically at 241 nm. Saturation solubility of pure drug was also determined.

In-vitro Dissolution Study

The dissolution studies of solid dispersions were performed using USP dissolution apparatus type I. Dissolution study was performed in 900 mL phosphate buffer pH 1.2. The stirring speed was 50 rpm, and the temperature was maintained at 37±0.5°C. The samples were withdrawn at 5, 10, 15, 30, 45 and 60 min and were replenished with fresh dissolution medium. The samples were filtered, diluted and analysed by UV spectrophotometer at 241 nm.

RESULTS AND DISCUSSION

Preformulation Studies

Solubility of the drug in water, methanol and chloroform was examined and found to be in conformity with pharmacopoeial specifications. **Table 1** explains the results of solubility studies.

Table 1: Solubility Profile of Drug.

Solvent	Solubility
Water	Practically insoluble
Methanol	freely soluble
Chloroform	Soluble

Melting point of the drug was found to be 115°C which is in conformity with the reported range. It indicates the purity of the drug sample.

IR spectrum of carvedilol was compared with the spectra of physical mixtures of carvedilol with the three different polymers used, (HPMC,-CD, and PVP K30). There was no disappearance of any characteristic peaks. This shows that there is no chemical interaction between drug and polymers used. The presence of characteristic peaks confirmed that the drug and polymers used were compatible [Figure 1].

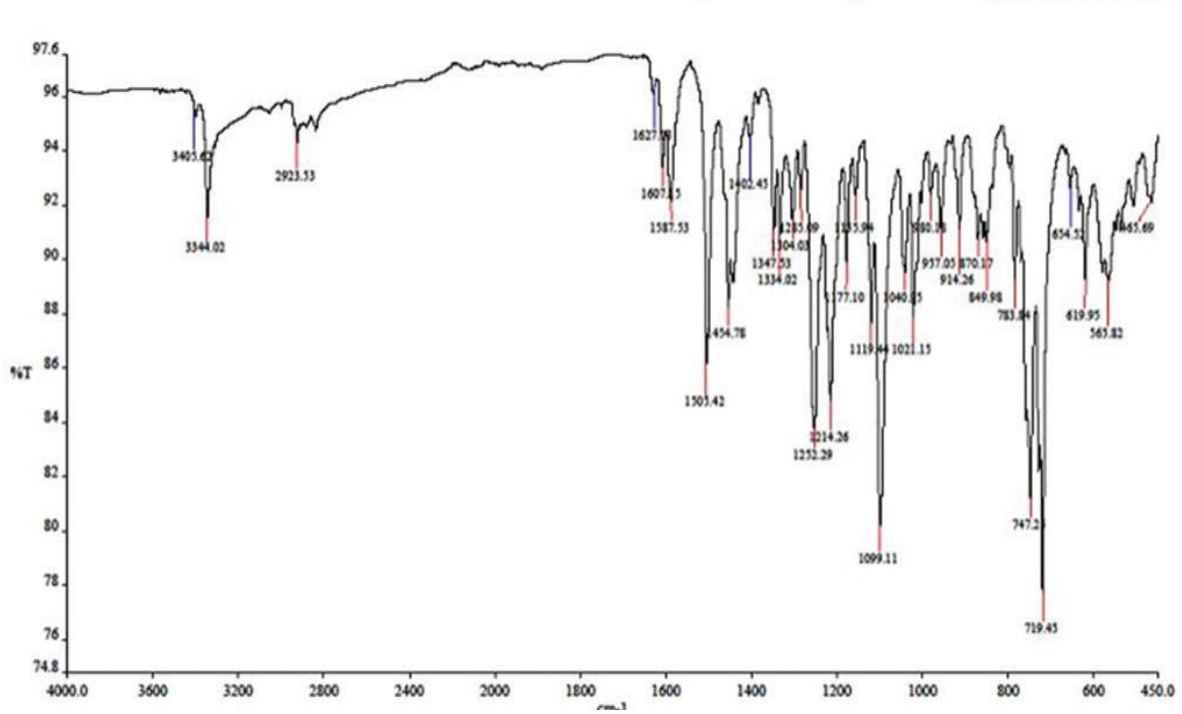


Figure 1: Infrared spectrum of Carvedilol+BCD-+PVP +HPMC.

Preparation of Solid Dispersion

Solid Dispersion Methods

Solid dispersions of Carvedilol-PVP K30, HPMC K100M, Beta cyclodextrin, were prepared by using three different methods (kneading method, melt solvent method, and co-precipitation method). The composition of verapamil solid dispersions is given below (Table 2):

Table 2: Composition of different solid dispersion formulations.

Code	Composition	Ratio	Method
F1 F2 F3	Carvedilol : PVPK30	1:1 1:2 1:3	Melt solvent method
F4 F5 F6	Carvedilol : BCD	1:1 1:2 1:3	Kneading method
F7 F8 F9	Carvedilol : HPMC K100M	1:1 1:2 1:3	Co-precipitation method

Table 3: Drug content and Percentage Yield of the Formulations F1–F9.

Formulation	Percentage Drug content	Percentage Yield
F1	96.96	94.4
F2	97.17	96.2
F3	98.42	93.6
F4	99.28	96.2
F5	99.64	97.8
F6	99.72	98.8
F7	98.91	97.4
F8	98.37	95.6
F9	98.61	98.1

Percentage Drug Release

Table 4: In-vitro Dissolution Profile of the Formulations F1–F9.

Time (min)	Percentage cumulative release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	49.18	50.85	54.80	58.63	63.92	67.06	59.06	62.30	64.00
10	60.59	61.38	63.96	67.58	73.43	76.02	65.58	69.35	74.65
15	68.75	69.47	70.76	79.40	80.81	85.53	78.12	78.85	79.94
20	72.82	77.55	78.84	85.78	88.71	90.36	84.93	85.38	86.74
25	79.54	80.93	82.52	90.08	93.60	95.17	89.66	90.36	92.17
30	87.77	88.90	89.56	94.75	95.16	96.75	92.24	94.32	95.22

The percentage drug content of solid dispersions was found to be in between 96.96 and 99.72%. All solid dispersion formulations showed the presence of high drug content. It indicates that the techniques are highly efficient for the preparation of solid dispersion. As it can be seen, all the formulations give a yield of above 90%, which is high enough to be used in tabulating purposes. The result of in-vitro dissolution study is given in the Tables 3 and 4. The percentage release at 30^{th} min of solid dispersions was within the range of 87.77–96.75%.

Saturation Solubility Study

The results of solubility and solubility enhancement ratio are given in Table 5.

Table 5: Results of saturation solubility study.

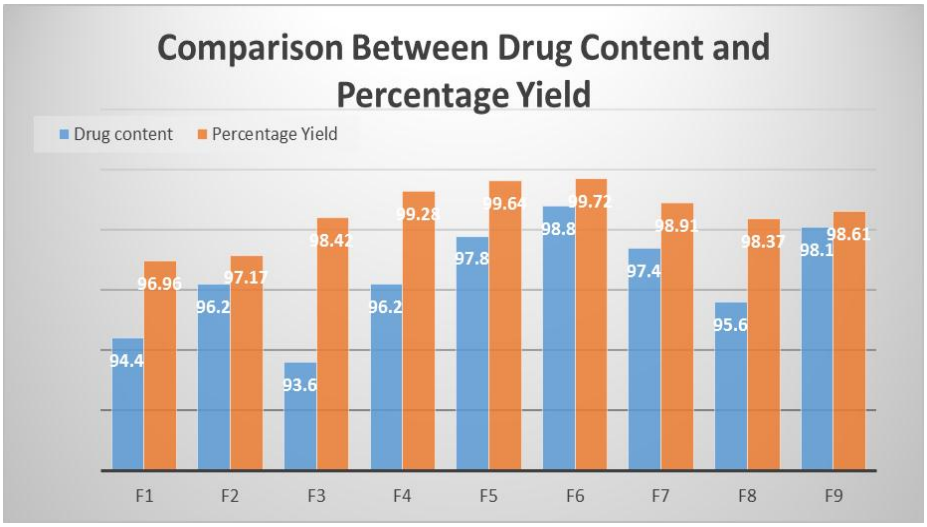
Formula Code	Solubility (mg/ml)	Enhancement Ratio
Pure Drug	0.0124	-
F1	0.0895	7
F2	0.1110	8
F3	0.1341	10
F4	0.1686	13
F5	0.1829	14
F6	0.1926	15
F7	0.1571	12
F8	0.1182	9
F9	0.1398	11

The results of the saturation solubility study showed that β-CD and HPMC were efficient carriers for solubility enhancement of poorly soluble drugs. Carvedilol showed 7-14 fold increase in the solubility.

Comparison between Drug content and Percentage Yield

The percentage drug content of solid dispersions was found to be in between 96.96 and 99.72%. All solid dispersion formulations showed the presence of high drug content. It indicates that the techniques are highly efficient for the preparation of solid dispersion. As it can be seen, all the formulations give a yield of above 90%, which is high enough to be used in tabulating purposes.

F6 formulation shows maximum drug content and percentage yield.



CONCLUSION

From this study, the increase in dissolution rates of carvedilol solid dispersions can be observed. Solubility studies showed a solubilizing effect of carriers on carvedilol. In these systems drug carrier interaction was shown with the use of FTIR. The dissolution rates of physical mixtures were higher than those of pure drug, which was possibly caused by increased drug wettability.

The Carvedilol-βCD/HPMC/PVP containing solid dispersions prepared by various methods. Formulation F6 showed faster drug release in comparison to other formulations. The present study conclusively indicated that the use of various solid dispersion methods by using water soluble carriers improved the solubility of poorly water soluble drug. It is clear from the data obtained that a higher polymer concentration gives faster drug release. Hence solid dispersion is one of most promising techniques used in enhancing the solubility of poorly water soluble drug.

REFERENCES

1. Dhirendra K, Lewis S, Udupan, et al. A Review on Solid Dispersion. Pak J Pharm Sci., Apr., 2009; 22(2): 234–246.
2. Reddy BB, Karunakar A. Biopharmaceutics classification system: A regulatory approach. Dissolution Technol, 2011; 2: 31-41.
3. Vishal Gupta, Madan AK, Rajesh Agarwal. Rapidly Soluble Tablets through Amalgamation of Cube Sugar and Solid Dispersion Technologies. Int J Pharm Front Res., Jul–Sep, 2011; 1(2): 1–13.
4. Kumari R, Chandel P, Kapoor A. Paramount Role of Solid Dispersion in Enhancement of Solubility. Indo Global J Pharm Sci., 2013; 3(1): 78–89.
5. Patel BP, Patel DM, Patel JK. A Review on Techniques which are Useful for Solubility Enhancement of Poorly Water Soluble Drugs. International Journal for Research in Management and Pharmacy (IJRMP), Dec., 2012; 1(1): 56–70.
6. Nadia Saffoon, Riaz Uddin, Naz Hasan Huda, et al. Enhancement of Oral Bioavailability and Solid Dispersion: A Review. Journal of Applied Pharmaceutical Science (JAPS), 2011; 01(07): 13–20.
7. Hind AlZein, Khalil Sakeer, Alanazi Fars K. Designing an Extended Release Waxy Matrix Tablets Containing Nicardipine-hydroxy Propyl β Cyclodextrin. Saudi Pharm J., 2011; (19): 245–253.

8. Chau Le-Ngoc Vo, Chulhun Park, Beom-Jinlee. Review Article on Current Trends and Future Perspectives of Solid Dispersions Containing Poorly Water Soluble Drugs. Eur J Pharm Biopharm, 2013; 85: 799–813.
9. Arun Raj R, Sruthy S Nair, Jyoti Harindaran. Formulation and Evaluation of Cyclodextrin Inclusion Complex Tablets of Carvedilol. Asian Journal of Pharmaceutics, 2016; 10(2): 84–94.
10. Ahmed Laith, Shaimaa N, Al Hammid Alaa, *et al.* Formulation and Evaluation of Flurbiprofen Solid Dispersion. *Int J Pharm Pharm Sci*., 2014; 6(2): 375–384.
11. Joda Altememy Dhiya R, Jaafar Jabir Altememy. Formulation and Evaluation of Meloxicam Liquisolid Compact. Int J Pharm Pharm Sci., 2014; 6(10): 453–463.
12. Arun Raj R, Das Anju C, Sreerekha S, et al. Formulation and Evaluation of Verapamil Solid Dispersion Tablets for Solubility Enhancement. Research and Reviews: A Journal of Pharmaceutical Science, 2016; 7(1): 39–54.
13. Anand Kumar Meka, Santhosh Pola, Karnaker Reddy Tupally, et al. Development, Evaluation and Characterization of Surface Solid Dispersion for Solubility and Dissolution Enhancement of Irbesartan. Int J Drug Dev Res., Jan–Mar, 2012; 4(1)1: 263–273.
14. Ankush Choudhary, Avtarc Rana, Geeta Aggarwal, et al. Development and Characterization of an Atorvastatin Solid Dispersion Formulation Using Skimmed Milk for Improved Oral Bioavailability. Acta Pharm Sin B., 2012; 2(4): 421–428.
15. Joda Altememy Dhiya R, Jaafar Jabir Altememy. Formulation and Evaluation of Meloxicam Liquisolid Compact. Int J Pharm Pharm Sci., 2014; 6(10): 453–463.