Enhancement of Solubility and Dissolution Rate of Poorly Water Soluble Clarithromycin Using Microwave Induced Fusion Method

[1]SHITAL A. KASTURE, [2]NILESH R. BHOSALE, [3] Dr. RAJASHREE CHAVAN, [4]ANKITA V. BHOSALE

[1,4]M. Pharm, Department of Pharmaceutics, PDEA's Seth Govind Raghunath Sable College of Pharmacy, Purandar (Saswad), Pune Maharastra 41230

[2]Assistant Professor, Department of Pharmaceutics, PDEA's Seth Govind Raghunath Sable College of Pharmacy, Purandar (Saswad), Pune Maharastra 41230.

[3]Principal, Department of Chemistry, PDEA's Seth Govind Raghunath Sable College of Pharmacy, Purandar (Saswad), Pune Maharastra 41230.

Abstract-The objective of the present work was to enhance the solubility and dissolution rate of the drug Clarithromycin, which is poorly soluble in water. Comparing the solubility of HPMC and PVP and HPMC show better result than PVP. The solubility of Clarithromycin was observed to increase with increasing concentration of hydroxypropyl methylcellulose.

The optimized ratio for preparing a solid dispersion (SD) of RLX with HPMC using the microwave-induced fusion method. Microwave energy was used to prepare SDs. HPMC was used as a hydrophilic carrier to enhance the solubility and dissolution rate of Clarithromycin. After microwave treatment, the drug and hydrophilic polymer are fused together, and the drug is converted from the crystalline form into an amorphous form. This was confirmed through scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and UV studies. These results suggested that the microwave method is a simple and efficient method of preparing SDs and solubility was found that 1:5 w/w. The solubility and dissolution rate of the SDs were increased significantly compared with pure Clarithromycin due to the surfactant and wetting properties of HPMC and the formation of molecular dispersions of the drug in HPMC. Conclusion-It was concluded that the solubility and dissolution rate of Clarithromycin are increased significantly when an SD of the drug is prepared using the microwave-induced fusion method.

Keyword- Clarithromycin, Solid Dispersion, Microwave-Induced Fusion Method, Solubility Enhancement.

INTRODUCTION

Drugs can be categorised into four classes using the Biopharmaceutical Classification System (BCS) based on their solubility and permeability. Low solubility and high permeability are characteristics of class II drugs. The rate-limiting stage in the absorption of a medicine from a solid dosage form is the low dissolution profile of relatively insoluble pharmaceuticals. To increase the dissolution rate, a variety of strategies can be helpful. The most common strategies include adding the medications to inert lipidic carriers such oils, surfactant dispersions, self-emulsifying formulations, and solid dispersions (SD) made from cyclodextrin inclusion complexes, polyvinylpyrrolidone, and polyethylene glycols 4000 and 6000.

For the preparation of SD, a novel strategy based on microwave irradiation has recently been presented.

A well-known method for heating and drying materials is microwave irradiation (MW). Microwaves can produce heat simultaneously in any place of the sample thanks to their capacity to penetrate any material. This is because it contains molecules with a dipolar moment that can absorb microwave radiation and turn it into heat. When the microwave frequency is quite close to the resonance frequency of the polar molecules, this event takes place. The ability of a particular substance to absorb microwave radiation determines how effectively materials can be heated by microwaves.

Microwave technology has recently gained a lot of popularity in organic chemistry. In contrast to conventional heating methods like conduction, convention, or infrared radiation, microwave radiation has a number of benefits like quick volumetric heating, no surface warming, addressable heating, energy savings, and cheap running costs. The absence of any risk brought on by leftover solvents is another major benefit of not employing organic solvents.

1 Physical approaches to solubility enhancement

The physical approach does not play with the structure of the drug molecule. In physical method, a drug molecule physically modulated by mean of any of the excipient added to it, such polymer for solid dispersion, or sometime particle size of drug is reduced to micron level to improve its solubility. The physical method includes particle size reduction, modification of drug crystal habits, drug dispersed into the hydrophilic carrier, complexation with cyclodextrin, and solubilization by using a surfactant molecule.(5)

1.1 Particle size reduction

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds. Useing traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level. Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Decreasing the particle size of these drugs, which cause increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.(6)

1.2 Solid dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy
of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), PlasdoneS630. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid dispersion.(7)

1.3 Self-emulsifying drug delivery system

The self-emulsifying drug delivery system is a lipid-based formulation that enhances the solubility and dissolution rate of the combined hydrophobic drug. The delivery system contains a mixture of oil (natural or synthetic lipids, surfactant, co-surfactant and co-solvent) the drug delivery system classically possesses self-dispersing ability as well as the capability to form O/W emulsion or micro emulsion after slight agitation. The disadvantages of the system are chemical instability of drugs, and some high use surfactant may cause gastro intestinal toxicity after oral administration.(8)

METHOD AND MATERIAL

Clarithromycin was purchased from Aarti pharmaceutical Mumbai, PVP, PHPMC research lab.

Preparation of Physical Mixture

Physical mixture of Clarithromycin and PVP and HPMC were prepared by mixing them in different ratios from 1:1 to 1:5 w/w simply by using mortar and

pestle. Ratio optimization was carried out using a solubility determination method.

Solid dispersion with different Clarithromycin and PVP and HPMC ratios from 1:1 to 1:5 w/w were prepared by using a microwave induced fusion method. Clarithromycin and PVP and HPMC were weighed in the ratio 1:1 and mixed gently for 5 minutes using a mortar and pestle. A fixed amount of the mixture was subjected to microwave radiations for different durations (3, 4, 5 and 6 minutes) at a constant power of 640 w in a microwave oven (LG 205 KMG5). Similarity, mixtures of other ratios from (1:2 to 1:5) were prepared. Only one beaker placed at a time inside the microwave oven. The samples were exposed to microwave radiation for predetermined durations (3, 4, 5, 6 minutes). Then beaker containing samples were maintained at room temperature for the samples to solidify. The solid dispersions were collected and placed in desiccators for 24hours and then product was pulverized using a mortar and pestle. The pulverized powders were passed through an 40# sieve.

Result

Drug Authentication

The UV Visible Spectrophotometer was also used to identify the drug. The medium used was methanol, and the observed and reported values of the absorption maxima were compared. The highest absorbance wavelength provides as an identifying property of a substance. The observed value for the pure clarithromycin sample that was obtained was 210 nm, and it was discovered to be identical to the claimed value, confirming the sample's identity as clarithromycin.

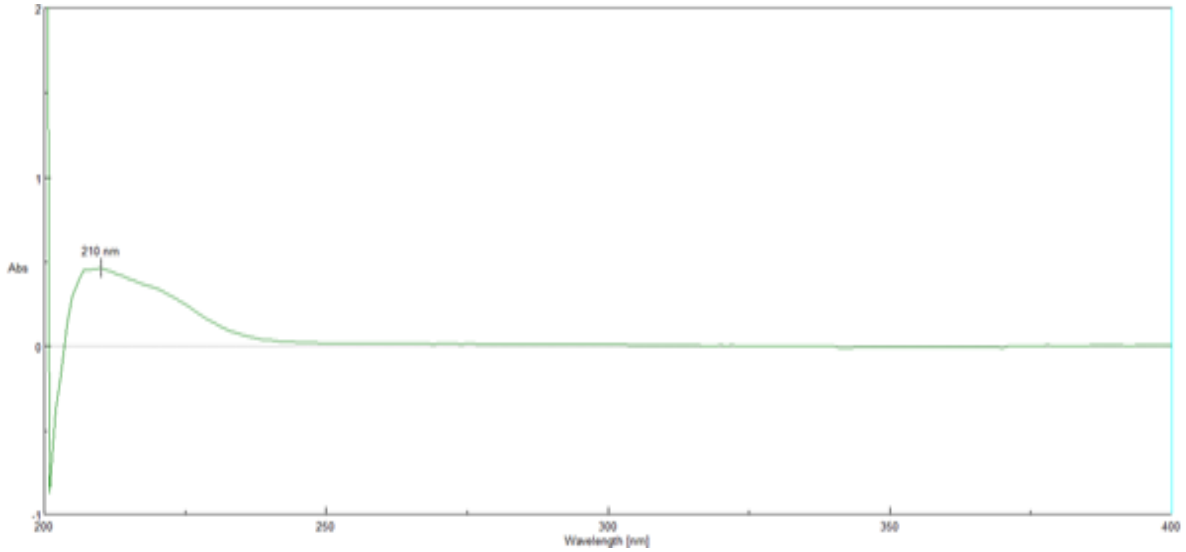


Fig No. 1 Drug Authentication by UV at 210 nm

Solubility enhancement

Method of microwave-induced fusion

Data in the table indicate that solid dispersion with an HPMC greatly improves solubility. A ratio change to 1:5 didn't significantly improve solubility. As a result, it was determined that the 1:5 ratio is ideal and was used to subsequent research. Optimized batch F5

Solubility of Glipizide in water is 0.0375 mg/ml.

Solubility of Glipizide in Phosphate buffer pH 7.4 is 0.0561 mg/ml.

For solubility determination excess amount of mixture dissolved in 10ml phosphatebuffer pH 7.4. Placed in rotary shaker for 24 hours. Filtered solution and taking absorbance of that solution without dilution.

y=mx + c or x=y-c/m (y=absorbance, m= slope, c= intercept values taken fromcalibration curve)

Divide ‘x’ value by 10 because we take 10 ml phosphate buffer pH 7.4.

Sr. No.	Drug Polymer Clarithromycin : HPMC	Solubility (mg/ml)
1	1:1	0.101
2	1:2	0.122
3	1:3	0.168
4	1:4	0.185
5	1:5	0.198
6	1:6	0.1

Scanning Electron Microscopy

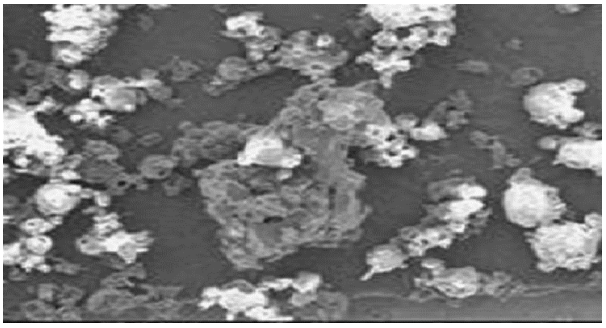


Fig No. 2 SEM analysis of clarithromycin: HPMC

Scanning electron microscopy give information there is conform of size reduction and better uniform distribution of drug particle. Scanning electron microscopy is ranges between 20 to 100 nm.

Differential scanning calorimetry (DSC)

DSC thermogram shows that there is no interaction between the drug and the polymers in the picture. Thermal research revealed that the current drug's DSC scan had a distinct extrapol peak at 230ºc. matching the temperature at which it transitions to melting. The physical drug mixture with all excipients' DSC thermogram displayed a distinctive extrapol peak at 228ºc with a declining melting point. The peak's intensity was reduced in the physical mixing of all excipients and drugs, and no new peaks were discovered. As a result, it was established that there is no interaction between the excipient and the drug.

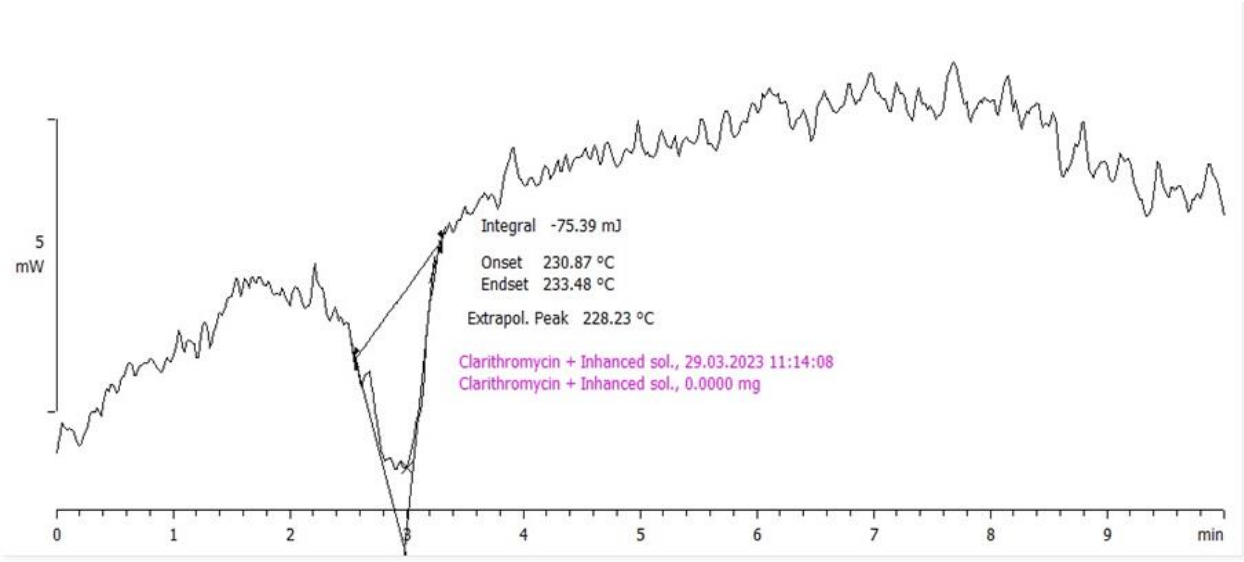


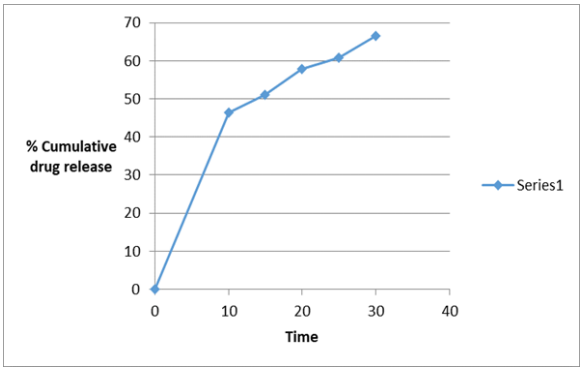
Fig No. 3 DSC of Clarithromycin : HPMC at melting point of 228. 23°C.

IN VITRO DRUG RELEASE

The dissolution rates of clarithromycin and different SDs were determined in 900 mL of pH 1.2 acetic at 37 °C ± 0.5 °C with a stirrer rotation speed of 75 rpm using the USP Dissolution Apparatus II (paddle type). Aliquots (5 mL) of the sample were withdrawn at 5, 10, 15, 30, 45, 60, 90, 105 and 120 minutes using a pipette. The samples were suitably diluted and assayed spectrophotometrically at 210 nm.

The dissolution profiles of clarithromycin and SDs prepared with exposure time of 3, 4, 5, 6 minutes from the dissolution profiles it is seen that the microwave – induced fusion technique improve the dissolution rate of clarithromycin to a great extent.

Product	% cumulative drug release
Clarithromycin	46.42 ± 2.11
Solid dispersion 3 min	50.98 ± 2.39
Solid dispersion 4min	57.75 ± 2.25
Solid dispersion 5 min	60.85 ± 1.28
Solid dispersion 6 min	66.48 ± 2.69



CONCLUSION

The unique aspect of this work is the creation of an amorphous system by the use of a microwave-induced approach that demonstrated both an impressive improvement in solubility and in vitro drug dissolution. As a result, it is stated that improving Clarithromycin's poor water solubility and dissolving rate by the use of the microwave-induced fusion method is a promising strategy. The surfactant and wetting capabilities of HPMC, as well as the creation of molecular dispersions of the drug in the polymer, may be responsible for increasing Clarithromycin's solubility and rate of dissolution in SDs.

REFERENCE

1. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm. Res. 12, 413–420.
2. Bergese, P., Colombo, I., Gervasoni, D., Depero, L.E., 2003. Microwave generated Nanocomposites for making insoluble drugs soluble. Mater. Sci. Eng. 23, 791–795.
3. Buhler, V., 2005. Vinylpyrrolidone-vinyl acetate copolymer (Copovidone). In: Buhler, V. (Ed.), Polyvinylpyrrolidone Excipients for Pharmaceuticals. Springer-Verlag, Berlin Heidelberg, Germany.
4. Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281–1302.
5. Cirri, M., Mura, P., Rabasco, A.M., Gines, J.M., Moyano, J.R., Gonzalez-Rodriguez, M.L., 2004. Characterization of ibuproxam binary and ternary dispersions with hydrophilic carriers. Drug Dev. Ind. Pharm. 30, 65–74.
6. Ford, J.L., 1986. The current status of solid dispersions. Pharm. Acta Helv. 61, 69–88.
7. Garekani, H.A., Sadeghi, F., Badiee, A., Mostafa, S.A., Rajabi-Siahboomi, A.R., 2001.
8. Crystal habit modifications of Ibuprofen and their physicomechanical characteristics. Drug Dev. Ind. Pharm. 27, 803–809.
9. Kappe, C.O., 2004. Controlled microwave heating in modern organic synthesis. Angew. Chem. Int. Ed. 43, 6250–6284.
10. Kerˇc, J., Srˇciˇc, S., Kofler, B., 1998. Alternative solvent-free preparation methods for felodipine surface solid dispersions. Drug Dev. Ind. Pharm. 24, 359–363.
11. Mallick, S., Pattnaik, S., Swain, K., De, P.K., Saha, A., Ghoshal, G., Mondal, A., 2008. Formation of physically stable amorphous phase of ibuprofen by solid state milling with kaolin. Eur. J. Pharm. Biopharm 68, 346–351.
12. Moneghini, M., Carcano, A., Zingone, G., Perissutti, B., 1998. Studies in dissolution enhancement of atenolol. Part I. Int. J. Pharm. 175, 177–183.
13. Nash, R.A., 1994. Cyclodextrins. In:Wade, A.,Weller, P.J. (Eds.), Handbook of Pharmaceutical Excipients, 2nd ed. American Pharmaceutica Association,Washington, and The Pharmaceutical Press, London, pp. 145–148.
14. Novoa, G.A.G., Heinamaki, J., Mirza, S., Antikainen, O., Colarte, A.I., Paz, A.S., Yliruusi, J., 2005. Physical solid-state properties and dissolution of sustained-release matrices of polyvinylacetate. Eur. J. Pharm. Biopharm. 59, 343–350.