Microwave Induced Solid Dispersion as a Novel Technique for Enhancing Solubility of Rifampicin

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Abstract

The aim of this work was to enhance the solubility of poorly soluble drugs like Rifampicin and further study the effect of enhanced solubility on the dissolution rate. Microwave induced solid dispersion is novel technique to enhance solubility of poorly soluble drugs. Rifampicin is Anti tuberculosis drug, used either in a combination with other drugs or without any combination. But as it belongs to BCS Class-II (low solubility & high permeability) it shows low bioavailability so the primary objective was to enhance solubility of Rifampicin.

The attempt was made to enhance a solubility of poorly water soluble drug Rifampicin by using Microwave Induced Solid Dispersion. HPMC E5LV was used as dispersion media for the solid dispersion. This study was involved preformulation study of drug, characterization of solid dispersion and evaluation of formulation.Solid dispersions were prepared by Kneading Method, Solvent Evaporation Method and Microwave Induced Method. Further optimization was performed to select optimum ratio of drug to polymer. Optimized solid dispersions were selected for a capsule formulation. Evaluation of solid dispersion & capsules were performed. The microwave-induced solid dispersion method is a promising approach to enhancing the solubility and dissolution rate of Rifampicin having low solubility in water.

KeyWords: Solid Dispersion, Rifampicin, Microwave, Electromagnetic, poorly soluble drugs
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Introduction

The oral route of drug administration is the most important route for administering drugs for systemic effects. When a new drug is discovered, one of the first questions that arise to a pharmaceutical research scientist is whether or not the drug can be effectively administered by oral route for its intended effect. The development of dosage forms especially for the prolonged release purpose has been a challenge to formulation scientists because of many independent factors governing the absorption of the drug from the gastrointestinal tract. For example, modifying the solubility of the drug substance to prolong its release in the gastrointestinal tract may cause a reduction in the overall dose of formulation.For this purpose the drug substances are categorized into four classes based on their solubility parameter and permeability to bio-membranes, and such a classification system is called as a Biopharmaceutical Classification System (BCS). The BCS was first devised in 1995, by Amidonet et al and since then it has become a benchmark in the regulation of bioequivalence of oral drug products. (1, 2, 3, 4)

Table 1.1 Biopharmaceutical Classification System (1, 5)

Class	Solubility	Permeability
Class-I	High	High
Class-II	Low	High
Class-III	High	Low
Class-IV	Low	Low

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Methods for Solubility Enhancement:

There are various methods of solubility enhancement which may affect physical or chemical properties of drug as enlisted below
Salt Formation 2. Micronization 3. Nano Suspension 4. Spray Drying
5. Lyophilization/Freeze-Drying Technique 6. Hydrotropy 7. Co-solvency
8. High Pressure Homogenization 9. Sonocrystallisation 10. Complexation
11. Liquisolid Technique 12. Micro-Emulsion
13. Self-Emulsifying Drug Delivery Systems
14. Polymeric Alteration
15. Solid Dispersion
Physical Mixture
Kneading Method
Melting method
Microwave Induced Solid Dispersion

Microwave Induced Solid Dispersion Method:

In this method the complex of drug & polymer is formed by using a microwave. When mixture of drug and polymer are kept in microwave radiation there is increase in heat at each & every part of the mixture and it causes a fusion of drug and polymer to form solid dispersion.(6, 7)
General advantages of Microwaves processing:
There is a considerable decrease in the processing time due to use of microwaves.
It produces uniform heating to the every point of the system.
Lower diffusion activation energy is required while using microwaves.
It also helps to enhance chemical reaction rates.
It has lower sintering temperature.(8)

Microwave induced solid dispersion method a novel approch of solubility enhancement:

Microwave induced solid dispersions appear to be a better approach to improve drug solubility than other methods, because they are easier to prepare and more use able.There are various methods of solid dispersion like kneading method, solvent evaporation method, melting method, hot melt extrusion, supercritical extraction, Microwave Induced fusion method have some extra benefits over other techniques of solid dispersion. (9, 10)
The use of microwaves (MW) presents attractive advantages in processing materials. MW heating is a consequence of the energy exchange of the electromagnetic (EM) field with the dielectric system (electro thermal coupling), and occurs through two classes of mechanisms: migration of ions and rotation of dipole molecules. Essentially, differences and advantages of MWs over conventional heating arise from this. This route to overcome solubility problems of water-insoluble drugs looked us exciting, since it sums the bioavailability advantages of a drug dispersion in a stabilizing suspension with the perspectives of an effective, energy saving and solvent-free approach.(11)
In conventional processing, heat is generated by an external heating source. Subsequently, thermal energy flows from the surface to the bulk of the material by thermal diffusion. On the contrary, in materials under MW flux, heat is generated at each point of the material by the interaction of the EM field with its molecular and electronic structure. The main consequences of these inherent differences are straightforward: heat generation by MW is uniform throughout the material volume, and heating doesn't depend on the material conductivity and it is more rapid, since thermal diffusion from the skin to the core of the material is skipped, the thermal gradient and the heat flow in MW processed materials are opposite to those in conventionally heated materials. (12)

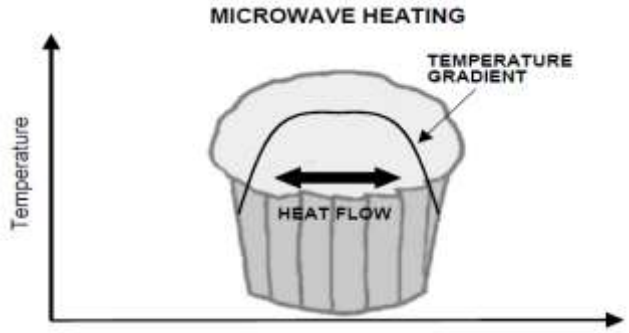

Fig 1.1 Temperature gradients and heat flows generated in materials by microwave heating

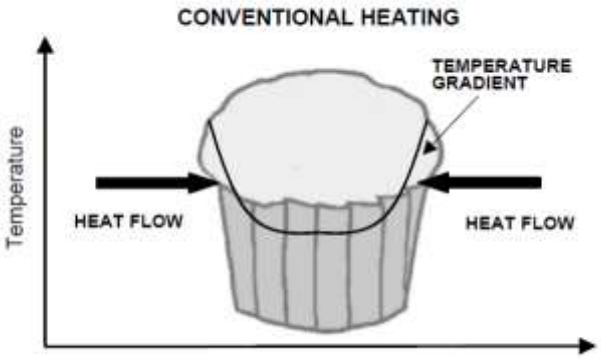

Fig. 1.2 Temperature gradients and heat flows generated in materials by conventional and microwave heating

Microwave induced solid dispersion imparts following properties of drug
Particles with reduced particle size
Particles with improved wettability
Particles with higher porosity
Drugs in amorphous state
Tuberculosis (TB) continues to pose as a global menace despite of a myriad of attempts worldwide. Moreover, the emergence of multiple drug resistant cases of TB and HIV co- infection are major threats to the control of the disease. Keeping in view that TB is a global emergency, the formulation research strategies should focus on overcoming the aforementioned challenges by adopting newer delivery approaches for anti TB drugs.
Rifampicin is the semi synthetic hydrazine derivative of Rifampicin B remains one of the classical first line drugs for TB. (13) Rifampicin belongs to the BCS class II (Low Solubility and high permeability) so the In vivo dissolution is the rate limiting step for its action. Due to poor solubility, Rifampicin shows poor bioavailability and to enhance the oral bioavailability of Rifampicin there is need to enhance its dissolution rate. It is proved that increasing solubility of drug can enhance dissolution rate of the drug so the strategy of this work was to enhance the solubility of Rifampicin. Microwave Induced solid dispersion have various advantages as mentioned above over the other strategies to enhance solubility of poorly water soluble drug so the attempt was made to enhance the solubility of Rifampicin by microwave induced solid dispersion method. (14)

MATERIALS AND METHODS

Drug candidate

We select Rifampician (Gift sample from Lupin LTD, Aurangabad.) as a drug candidate having slightly to very slightly solubility in water (15) & 68 % Bioavailability. (16, 17)

Dispersion Medium

We select HPMC E5LV (Analab fine chemicals, Mumbai.) as a dispersion medium. Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulation. (18, 19)

Preparation of solid dispersion by MW Induced Solid Dispersion method:

Weighed quantity of Rifampicin and HPMC E5LV were mixed together to make different ratios as 1:1, 1:2, and 1:3 (w/w) followed by gentle mixing in mortar & pestle. Fixed amount of these mixtures were subjected to Microwave for 2 min, 4 min, 6 min at different power of Microwave radiation (100 W, 180 W, 300 W) in a microwave oven as shown in following table 1.1. Beakers were then allowed to cool at room temperature for 24 hours. After 24 hours these mixtures were triturated in mortar and passed through sieve no. 80 and stored in desiccator for further study. (20, 21)

Table 1.1 Solid dispersions prepared by Microwave Induced Method.

Sr. no.	Formulation code	Microwave Power	Rifampicin: HPMC Ratio	Time
1	MRH 1	100 W	1:1	2 min
2	MRH 2	100 W	1:1	4 min
3	MRH 3	100 W	1:1	6 min
4	MRH 4	100 W	1:2	2 min
5	MRH 5	100 W	1:2	4 min
6	MRH 6	100 W	1:2	6 min
7	MRH 7	100 W	1:3	2 min
8	MRH 8	100 W	1:3	4 min
9	MRH 9	100 W	1:3	6 min
10	MRH 10	180 W	1:1	2 min
11	MRH 11	180 W	1:1	4 min
12	MRH 12	180 W	1:1	6 min
13	MRH 13	180 W	1:2	2 min
14	MRH 14	180 W	1:2	4 min
15	MRH 15	180 W	1:2	6 min
16	MRH 16	180 W	1:3	2 min
17	MRH 17	180 W	1:3	4 min
18	MRH 18	180 W	1:3	6 min
19	MRH 19	300 W	1:1	2 min
20	MRH 20	300 W	1:1	4 min
21	MRH 21	300 W	1:1	6 min
22	MRH 22	300 W	1:2	2 min
23	MRH 23	300 W	1:2	4 min
24	MRH 24	300 W	1:2	6 min
25	MRH 25	300 W	1:3	2 min
26	MRH 26	300 W	1:3	4 min
27	MRH 27	300 W	1:3	6 min

Preparation of solid dispersion by kneading method:

Weighed quantity of Rifampicin and HPMC E5LV were mixed together to make different ratios as shown in table 1.2. Then these mixtures were added to mortars and triturated with small quantity of Methanol to prepare slurries. The prepared slurries were then air dried at 25oC for 24hrs. The resultant products were pulverized and passed through sieve no. 80 and stored in desiccator for further studies. (22)

Table 1.2 Solid dispersions prepared by kneading method

Sr. no.	Formulation Code	Rifampicin: HPMC Ratio
1	KRH 1	1:1
2	KRH 2	1:2
3	KRH 3	1:3

Preparation of solid dispersion by solvent evaporation method:

Weighed quantity of Rifampicin and HPMC E5LV were mixed together to make different ratios as 1:1, 1:2, and 1:3 (w/w). Then these mixtures were dissolved in Methanol as it is a common solvent for both Rifampicin & HPMC E5LV. These solutions of Rifampicin & HPMC E5LV in methanol were allowed for evaporation for 24 hours. After 24 hours there was formation of a film of Rifampicin & HPMC E5LV. These films were triturated to make powder of it. Powder was passed through sieve no 80 and stored in desiccator for further studies. (23)

Table 1.3 Solid dispersions prepared by Solvent Evaporation Method.

Sr. no.	Formulation code	Rifampicin: HPMC E5LV Ratio
1	SRH 1	1:1
2	SRH 2	1:2
3	SRH 3	1:3

Assay of optimized solid dispersions

Solid dispersions equivalent to 10 mg of Rifampicin were weighed and transferred to 100 ml volumetric flask, 80 ml of methanol was added to it and shaken. Volume was made up with methanol and filtered it with whatman filter paper by discarding first 20 ml of filtrate. 2 ml of filtrate diluted to 100 ml of buffer and absorbance was measured. Same procedure was repeated by replacing solid dispersions with Rifampicin to calculate drug content of solid dispersions.

Preparation of Capsules:

Solid dispersions prepared by each method were weighed accurately equivalent to 150mg of Rifampicin and mixed with sodium starch glycolate. Then magnesium stearate was added to it before capsule filling. Blend was filled in empty capsule shell by using capsule filling machine. These capsules were stored in desiccator & used for further evaluation study. (24)

Table 1.4 Formulation of capsule

Sr. no.	Capsule Formulation Batch Code	Contents				
		Rifampicin IP (mg)	Solid Dispersions (mg)	Sodium Starch Glycolate (mg)	Lactose (mg)	Magnesium Stearate (mg)
1	PDC	150	-	8	300	2
2	KMC	-	450	8	-	2
3	SMC	-	450	8	-	2
4	MMC	-	450	8	-	2

Result And Discussion

The aim of the study was to enhance a solubility of Rifampicin by using microwave induced solid dispersion; HPMC E5LV was used as polymer for solid dispersion. Solid dispersions were prepared by Kneading Method, Solvent Evaporation Method and Microwave Induced Method. Further optimization was performed to select optimum ratio of drug to polymer. Optimized solid dispersions were selected for a capsule formulation. Evaluation of solid dispersion & capsules were performed.

Preformulation study

FTIR study of pure drug-

The FTIR spectra of pure Rifampicin was taken by KBr disc method. The peaks found were as follows-

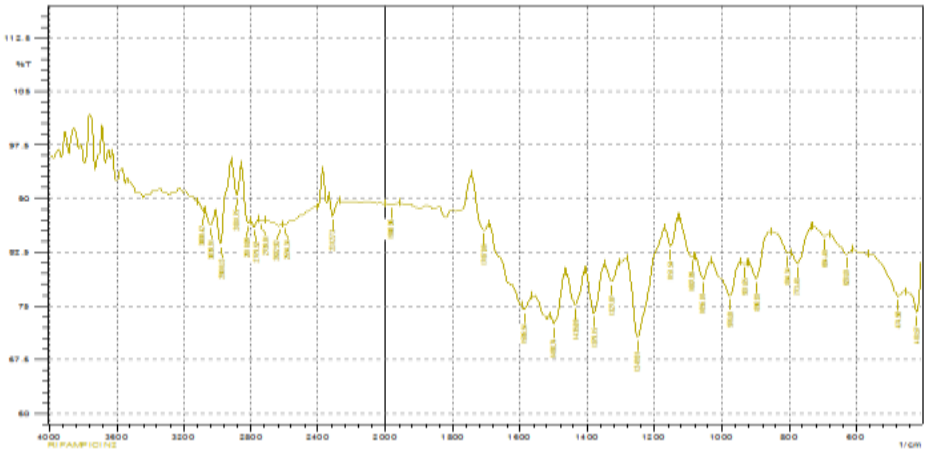

Fig 1.3 FTIR Spectra of Rifampicin

Table 1.5 IR Study of Rifampicin.

Sr no	Peak Observed	Functional Group
1	3080.42 cm-1	O–H, N-H
2	2980.12 cm-1	C-H stretching
3	1707.06 cm-1	-C=O acetyl stretching
4	1585 cm-1	-C=N asymmetric stretching
5	1498.74 cm-1	C=C Stretching
6	1379.15 cm-1	C-N Stretching
7	1249.91 cm-1	-C-O-C- ether group
8	976.01 cm-1	C=C Bending

The FTIR spectrum of pure rifampicin showed its several characteristic peaks; absorption band of O-H and N-H at 3080.42 cm-1, the C-H stretching at 2980.12 cm-1, -C=O acetyl stretching at 1707.06 cm-1, -C=N asymmetric stretching at 1585 cm-1, C=C stretching at 1498.74 cm-1, C-N stretching at 1379.15 cm-1, –C-O-C- ether group at 1249.91 cm-1and C=C bending at 976.01 cm-1.

Melting Point

Melting point of rifampicin was observed as follows;

Table 1.6 Melting point of Rifampicin.

Sample	Reported	Observed ºC ±SD
Rifampicin	183 ºC	183.83 ºC ±0.7638

All values are expressed as mean ±SD, n=3

Calibration Curve of Rifampicin

The standard stock solution of Rifampicin was prepared in water. The absorbance values are given in table 1.7 and standard plot of Rifampicin is shown in figure 1.4. The curve was found to be linier in Beer's range at 0-25 µg/ml at 475 nm. Values found were as follows-

R2 = 0.998 Intercept- 0.0108 Slope- 0.0042

Table 1.7. Calibration curve for Rifampicin.

Concentration(µg/ml)	Absorbance ±SD
0	0
5	0.0472 ± 0.0023
10	0.0985 ± 0.0152
15	0.1589 ± 0.0229
20	0.2196 ± 0.0230
25	0.2682 ± 0.0340

All values are expressed as mean ±SD, n=3

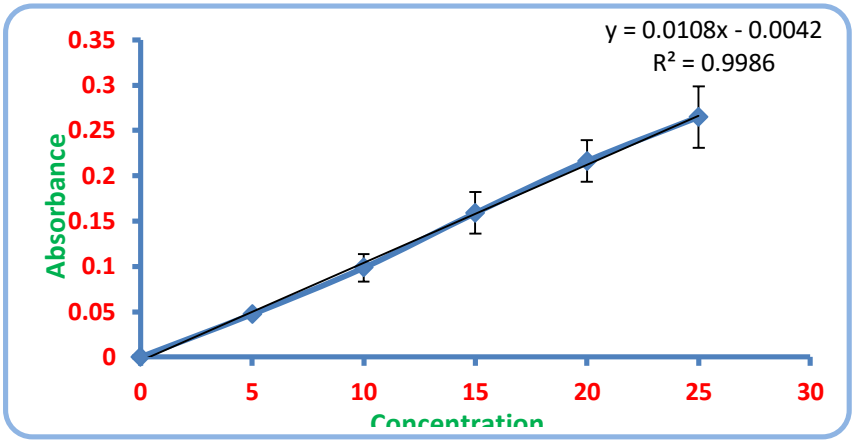

Fig 1.4 Calibration Curve of Rifampicin.

Solubility study

Solubility study of drug was done in water and buffer and the results obtain were as follows;

Table 1.8 Solubility studies of Rifampicin in different solvents

Solvent	Solubility (mg/ml)
Water	1.2706 ±0.0042
Buffer	1.3578 ±0.0970

All values are expressed as mean ±SD, n=3

Preparation and solubility study of solid dispersions by Microwave Induced Solid Dispersion method

Solid dispersions of Rifampicin and HPMC E5LV were prepared by using Microwave Induced Fusion method as shown in table 1.1 and the solubility study was performed to select optimum ratio. The solubility results are as shown below in table 1.9. When solubility of solid dispersions prepared by microwave induced solid dispersion method compared with solubility of pure drug, formulation MRH 26 showed maximum solubility.

Table 1.9 Solubility studies of solid dispersions by MW Induced Solid Dispersion method.

Sr. No	Formulation	Solubility (mg/ml)
1	MRH 1	1.2882 ± 0.0133
2	MRH 2	1.3128 ± 0.0140
3	MRH 3	1.3412 ± 0.0107
4	MRH 4	1.4412 ± 0.0106
5	MRH 5	1.5536 ± 0.0118
6	MRH 6	1.5199 ± 0.0081
7	MRH 7	1.8596 ± 0.0109
8	MRH 8	1.8456 ± 0.0041
9	MRH 9	1.7413 ± 0.0033
10	MRH 10	1.3867 ± 0.0036
11	MRH 11	1.5469 ± 0.0107
12	MRH 12	1.5744 ± 0.0098
13	MRH 13	1.6017 ± 0.0069
14	MRH 14	1.6744 ± 0.0094
15	MRH 15	1.6315 ± 0.0150
16	MRH 16	1.8859 ± 0.0133
17	MRH 17	2.0734 ± 0.0101

18	MRH 18	1.9677 ± 0.0176
19	MRH 19	2.0912 ± 0.1097
20	MRH 20	2.4320 ± 0.0127
21	MRH 21	2.2978 ± 0.0096
22	MRH 22	2.3412 ± 0.0108
23	MRH 23	2.6006 ± 0.0222
24	MRH 24	2.5118 ± 0.0205
25	MRH 25	2.3667 ± 0.0287
26	MRH 26	2.7418 ± 0.0127
27	MRH 27	2.6736 ± 0.0127

All values are expressed as mean ±SD, n=3

Selection of the optimum ratio from each method:

As the aim of the study was to enhance a solubility of drug, optimum ratios have to be selected on the basis of their solubility. But due to physical inconvenience that is the volume of the ratio 1:3 would not be fitted in a available capsule size so though ratio 1:3 shows maximum solubility, ratio 1:2 were selected for further study as shown in table 1.12.

Table 1.12 Formulations selected for further study.

Sr no.	Method	Formulation selected	Solubility (mg/ml) ±SD
1	MW Induced Solid Dispersion	MRH 23	2.6006 ± 0.0222
2	Kneading Method	KRH 2	1.4998 ±0.0145
3	Solvent Evaporation	SRH 2	1.7582 ±0.0136

All values are expressed as mean ±SD, n=3

Assay of the optimized solid dispersions:

Assay of selected optimized ratios were performed to know the drug content of solid dispersions. Results found are shown below in table 1.13

Table 1.13 Assay of the optimized solid dispersion.

Sr no	Formulation	% Drug Content ±SD
1	MRH 23	98.77 ±0.7735
2	KRH 2	97.88 ±0.3553
3	SRH 2	99.10 ±0.3794

All values are expressed as mean ±SD, n=3

Preparation and evaluation of capsules

Preparation of capsule was performed as shown in table 1.4. PDC was prepared with pure drug and lactose as filler. The evaluation parameters are as below-

Evaluation of powder before feeling in capsule:

The flow ability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of capsule, otherwise, high dose variations will occur. The blends of different formulations were evaluated for angle of repose, bulk density, tapped density compressibility index and their results are as shown below in table 1.14.

Table 1.14 Evaluation of powder before feeling in capsule.

Formulation	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Carr's Index (%)	Housnar's Ratio	Angle of repose (θ)

MMC	0.7738 ±0.028	0.9038 ±0.019	14.40 ±1.29	1.1683 ±0.038	27.99 ±1.41
KMC	0.7817 ±0.024	0.9496 ±0.020	18.69 ±2.54	1.2307 ±0.017	29.26 ±0.18
SMC	0.8243 ±0.015	0.9496 ±0.020	13.15 ±3.06	1.1523 ±0.040	26.43 ±2.02

Evaluation of capsule

Evaluation of capsule for following parameters was performed and results found are as shown below-
Weight Variation test:

The % weight variation of all formulations was within 6.5% according to Indian Pharmacopoeia so it passes weight variation test.

Table 1.15 Weight variation test for capsules

Sr no	Capsule Code	% Weight variation
1	MMC	96.79 – 104.08
2	KMC	97.09 – 105.36
3	SMC	97.73 – 103.50

Active drug content

All the formulation were within a range 92.5 – 107.5 % (Indian Pharmacopoeia) so passes content uniformity test.

Table 1.16 Active drug content test for capsules

Sr no	Capsule Code	% Content ±SD
1	MMC	104.74 ±0.3902
2	KMC	96.27 ±1.0378
3	SMC	103.43 ±0.3842

All values are expressed as mean ±SD, n=3

Disintegration test:

Table 1.17 Disintegration tests of capsules

Sr no.	Capsule Code	Disintegration Time (Min) ±SD
1	MMC	5.50 ±0.5477
2	KMC	5.34 ±0.5163
3	SMC	5.17 ±0.4082

All values are expressed as mean ±SD, n=6

KMC capsule, SMC capsule, MMC capsule & marketed capsule.

In- Vitro Drug Release Data:

Comparison release data of untreated drug capsule,

Time (Mins)	% Drug Release				
	PDC Capsule	KMC Capsule	SMC Capsule	MMC Capsule	Marketed Capsule
9	15.98 ±0.3436	17.02 ±0.7878	16.55 ±0.9317	20.13 ±0.5825	43.70 ±0.3774
18	56.22 ±1.0210	62.45 ±3.4459	60.18 ±0.4821	57.70 ±0.4993	71.93 ±0.7830
27	66.15 ±3.6864	66.92 ±0.7903	61.93 ±0.6968	73.03 ±0.4264	80.60 ±0.6378
36	71.65	75.40	78.23	90.03	88.42

	±0.6552	±3.6660	±1.1324	±0.4821	±0.1500
45	75.97 ±0.5408	79.80 ±2.7372	82.83 ±0.7660	94.28 ±1.9998	89.50 ±0.5629

All values are expressed as mean ±SD, n=3

The comparison study of untreated drug capsule, KMC capsule, SMC capsule, MMC capsules and marketed was studied using IP Apparatus No. 2 in 0.1 N HCl. PDC shows 75.97 % release, KMC capsules shows 79.80 % release, SMC capsule shows 82.83 %, MMC capsule shows 94.28 % release and marketed capsule shows 89.50 % for 45 mins. From comparison study shows that MMC capsule shows greater release as compared to other capsules of Rifampicin. The graph is shown below in Fig 1.5.

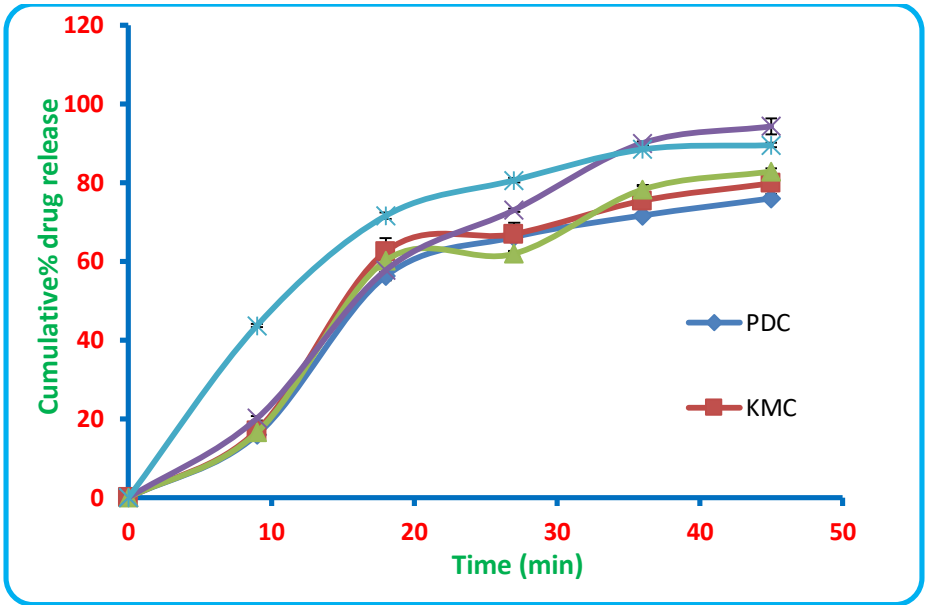

Fig 1.5 Comparison release data of PDC capsule, KMC capsule, SMC capsule, MMC capsule & marketed capsule.

Compatibility between drug and excipients-

The compatibility and interactions between drug and excipients were checked using Fourier transform infra-red (FTIR) spectroscopy and result obtained were as follows-

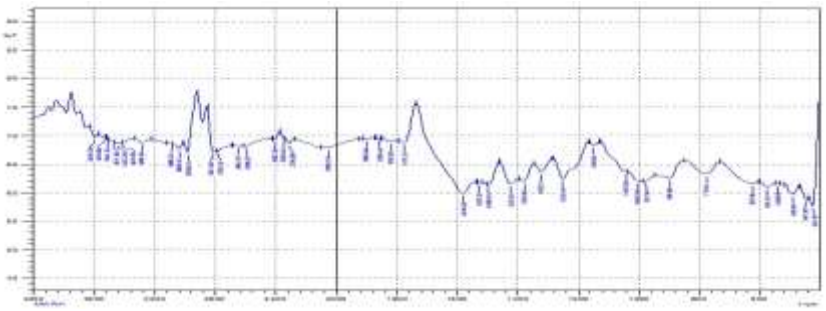

Fig 1.6 FTIR Spectra of a MMC formulation.

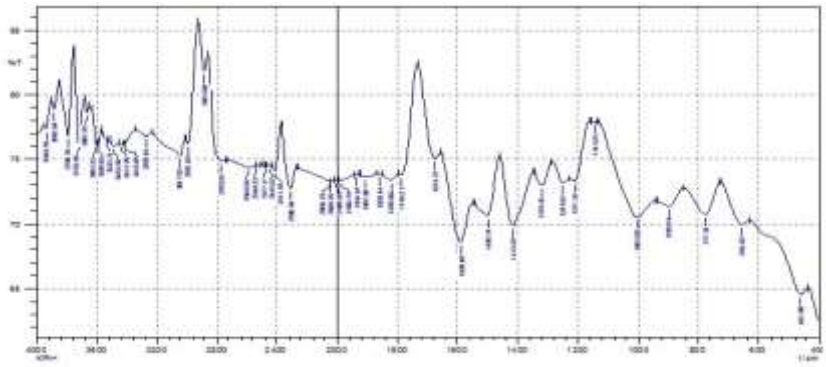

Fig 1.7 FTIR Spectra of a KMC formulation.

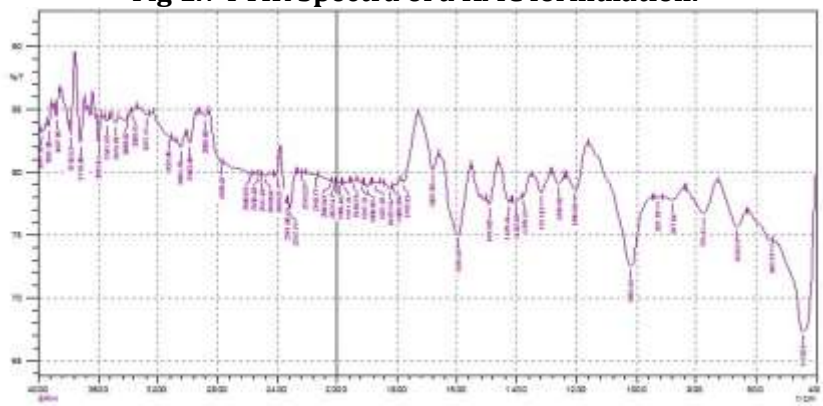

Fig 1.8 FTIR Spectra of a SMC formulation.

To study the possible interactions between Rifampicin, with excipients, IR spectra of blend was compared with the pure drug spectra. The blend showed almost the same characteristic peaks of drug indicating no interaction in the spectra almost of the formulation. N-H and O-H stretching of Rifampicin was little shifted towards higher wavelength and the other peaks are almost the same. This indicated that overall symmetry of the molecule is not significantly affected.

Stability studies

The MMC formulation was subjected to stability study. Stability study was conducted at 40ºC and 25ºC to investigate the effect of temperature on physical parameter of the formulation for 1 month.

Conclusion

Knowing that Rifampicin has low solubility in water, an attempt was made to increase its solubility and dissolution by highly promising microwave induced solid dispersion. The novelty of this work is the generation of solid dispersions, using the microwave-induced technique that showed a remarkably increased solubility as well as in vitro drug dissolution.

Therefore, it is concluded that the use of the microwave-induced solid dispersion method is a promising approach to enhancing the solubility and dissolution rate of Rifampicin having low solubility in water. The mechanism involved in enhancing the solubility and dissolution rate of Rifampicin in microwave induced may be attributed to the surfactant and wetting properties of HPMC E5 LV and the formation of solid dispersion dispersions of the drug in the polymer.

Conflict Of Interest

The authors have no conflicts of interest regarding this investigation.

References

Brahmankar D.M. et al, Bio pharmaceutics and Pharmacokinetics 2009; 349-357.

Khan, GM. Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems. The Sci. 2001, 1,350-354.

Amidon, GL, Lennerlas, H., Shah, VP, Crison, JR. A theoretical basis for a biopharmaceutics drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 1995, 12,413-420.

Dressman, J.; Butler, J.; Hempenstall, J.; Reppas, C. The BCS: Where Do We Go from Here? Pharm. Technol. 2001, 7, 68-76

Amidon GL, Lennearnas H, Shah VP, Crison R. A theoretical basis for biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 1995; 12: 413-420.

Zawar L R., Bari S B. Preparation, Characterization and In vivo Evaluation of Antihyperglycemic activity of Microwave generated Repaglinide Solid Dispersion, Chem.Pharm.Bull., 60 (4): 482–487, 2012.

Moneghini, M., Bellich, B., Baxa, P., Princivalle, F. Microwave generated dispersions containing Ibuprofen, Int. J. Pharm., 361: 125–130, 2008.

Booske JH, Cooper RF, Dobson I. Mechanisms for nonthermal effects on ionic mobility during microwave processing of crystalline solids. J. Mat. Res. 1992; 7, 2 : 495-501.

Committee on microwave processing of materials: an emerging industrial technology. Microwave processing of materials, Publication NMAB-473. Washington: National academy Press, 1994.

Ponne CT, Bartels PV. Interaction of electromagnetic energy with biological material – relation to food processing. Radiat. Phys. Chem. 1995 ; 45, 4: 591-607.

Lee KY. Microwave processing of ceramics and ceramic composites using a single-mode microwave cavity. PhD thesis, Michigan State University, Department of Materials Science and Mechanics, 1998.

evaluation of solid dispersion of atrovastatin calcium, Journal of pharmaceutical and scientific innovation, 2013.

PayalHasmukhlal Patil, Veena SailendraBelgamwar, Pratibha Ramratan Patil, Sanjay Javerilal Surana; Enhancement of solubility and dissolution rate of poorly water soluble raloxifene using microwave induced fusion method, Brazilian Journal of Pharmaceutical Sciences vol. 49, n. 3, jul./sep., 2013.

Nikam SP, A Review: Increasing Solubility of Poorly Soluble Drugs, by Solid Dispersion Technique. Research Journal of Pharmacy and Technology.4 (12); Dec.2011:1933-1940.

Sareen S, Mathew G, Joseph L. Improvement in Solubility of Poor Water-Soluble Drugs by Solid Dispersion. International Journal of Pharmaceutical Investigation: Review Article.2 (1); 2012:12-17.

Lachman L, Lieberman H and Kanig J L, The theory and Practice of Industrial Pharmacy, 3rd edition, Lea &Febiger, 1986 pg no. 151-158.

Rybakov KI, Semenov VE. Possibility of plastic deformation of an ionic crystal due to the nonthermal influence of a high-frequency electric field. Phys. Rev. B. 1994; 39, 1: 64-68.

Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. Respir Res, 2001; 2(3):164-168.

Balvinder Dhillon, Narendra Kr. Goyal, Rishabha Malviya and Pramod K. Sharma; Poorly Water Soluble Drugs: Change in Solubility for Improved Dissolution Characteristics a Review, Global Journal of Pharmacology 8 (1): 26-35, 2014

Wehrli, W., Knüsel, F., Schmid, K., Staehelin M., 1968. Interaction of rifamycin with bacterial RNA polymerase. Proc. Natl. Acad. Sci. 61, 667 73.

Abs- Kebrele, H., 1970. Physicochemical factors of drugs affecting absorption, distribution, and excretion. Acta Pharma. 30-47.

Nahata, M.C., Fan-Hovard, P., Barson, W.J., Bartkowski, H.M., Kosnik, E.J., 1990. Pharmacokinetics, cerebrospinal fluid concentration and safety of intravenous rifampicin in pediatric patients undergoing shunt placements. Eur. J. Clin. Pharmacol. 38, 515-517.

Niazi, Sarfaraz (2004). Handbook of Pharmaceutical Manufacturing Formulations.

Williams RO, Sykora MA, Mahaguna V (2001). "Method to recover a lipophilic drug from hydroxypropyl methylcellulose matrix tablets". AAPS Pharm.Sci.Tech. 2 (2): E8. doi:10.1208/pt020208.

Monica Sharma, Rajiv Garg, GD Gupta; Formulation and