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AN APPROACH TO INCREASE THE SOLUBILITY OF RIFAMPICIN BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Most of the drugs are weakly acidic and weakly basic with poor aqueous solubility. Hence various techniques are used for the improvement of the solubility of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. The purpose of this work was to describe the enhance solubility of rifampicin by using solid dispersion technique and Physical mixture with PEG6000. Here drug and carrier ratio 1:1, 1:2, 1:3 and 1:10 respectively. The prepared samples were evaluated by SEM, Drug content, *In-vitro* studies, Wettability and Solubility, IR studies, Angle of repose. *In-vitro* drug release showed fast and complete release over a period of 2hrs in pH7.4 release profile of solid dispersion (SD 10) were compared with pure drug and physical mixture. It was confirmed that no interaction between drug and polymers in the formulated solid dispersions by IR Spectra.

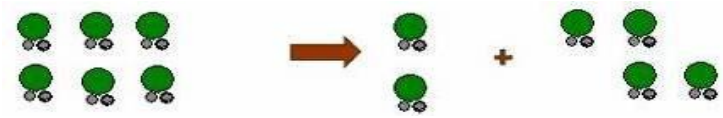
INTRODUCTION: Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Currently, only 8% of new drug candidates have both high solubility and permeability [1].

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature [2]. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water [3]. Solubility definitions are;

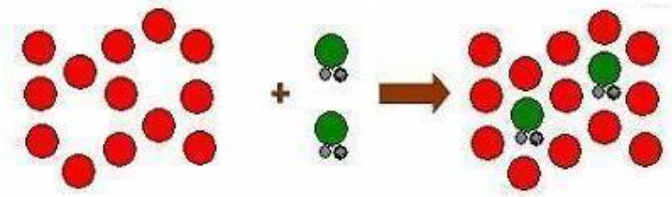
Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

The process of solubilisation involves the breaking of inter-ionic or intermolecular 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 [4].

STEP 1: HOLES OPENS IN THE SOLVENT



STEP 2: MOLECULES OF THE SOLID BREAKS AWAY FROM THE BULK



STEP 3:THE FREED SOLID MOLECULE IS INTERGRATED INTO THE HOLE IN THE SOLVENT

The solubility depends on the physical form of the solid (Particle size, Molecular size Polymorphs), the nature and composition of solvent medium (Polarity) as well as temperature and pressure of system[4]. There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are [5]:

1. **Physical Modifications** (Particle size reduction, Micronization, Nanosuspension Modification of the crystal habit, Polymorphs, Pseudopolymorphs, Drug dispersion in carriers, Eutectic mixtures, Solid dispersions, Solid solutions, Complexation, Use of complexing agents, Solubilization by surfactants, Microemulsions, Self microemulsifying drug delivery systems**.**

2. **Chemical Modifications.** The Rifampicin is a semisynthetic derivative of rifampicin B. It has a broader antimicrobial activity and had found application in the treatment of a number of different bacterial infections (Mainly used in tuberculosis). It is soluble in water at acidic pH and soluble in organic solvents like methanol, ethanol, chloroform, acetone and its solubility 1.4mg/ml to enhance upto 4.13e-02g/l [6].

   The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method [7]. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone [8, 9], polyethylene glycol [10], Plasdone-S630 [11]. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used [11].

In present work aims to enhance the solubility of the rifampicin by using Solid dispersion method and Physical mixture with PEG6000.

MATERIAL AND METHODS: Rifampicin was obtained as gift sample from Unichem Laboratories, Mumbai. PEG 6000, 4000, Ascorbic acid were obtained from West coast Laboratories, Mumbai. Potassium dihydrogen Ortho Phosphate, Methanol, Sodium Hydroxide were procured S.D. Fine Chem. Ltd, Mumbai, India.

Preparation of Solid Dispersions and Physical Mixture

Preparation of Solid Dispersions: Solid dispersions containing rifampicin were prepared by using PEG as coat material employing common solvent method. Four batches with drug to carrier (PEG6000) ratios namely 1:1,1:2,1:3 and 1:10 were prepared for the preparation of solid dispersions. The respective amount of carrier was dissolved in 50ml methanol taken in conical flask to get a clear complete soluble polymer solution. The weighed amount of rifampicin was added to this solution with constant stirring until the drug is completely incorporated in solvent. The solvent was removed by evaporation at room temperature. The mass obtained were further dried in desiccator for overnight, crushed and pulverized. Details are tabulated in the **Table 1.**

Preparation of Physical mixture: Drug carrier ratio of 1:10 was used to prepare physical mixture. The drug and carrier were mixed thoroughly in a mortor. This was done by geometric dilution technique to ensure homogenous distribution. Details are tabulated in the **Table 1**.

Evaluation of Solid Dispersions:

Sem Analysis [12]: The particle size, shape and surface morphology of solid dispersions were examined by scanning electron microscopy. (LEO, 435VP, UK) prior to examination, samples were mounted on an aluminium stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 20nm) in vacuum. The scanning electron microscope was operated an acceleration voltage of 15KV (**Figures 1, 2)**

Estimation of Drug Content in Solid Dispersion: 50mg solid dispersions or physical mixture were weighed accurately and transferred into a 50ml volumetric flask. The volume was made up to the mark with methanol and kept for 2hrs with occasional shaking and filtered. Then the drug content was analyzed Spectrophotometrically at 475nm using a single beam visible U.V.Spectrophotometer.

***In-Vitro* Dissolution Studies:** The release of rifampicin from solid dispersion was investigated in phosphate buffer of pH 7.4 as a dissolution medium (900ml) using the paddle method specified in USP X XIV (model TD T6P-Electrolab). Sample of 100mg solid dispersions were taken in the basket. A speed of 75 rpm and temperature 37±0.5°C was maintained throughout experiment. At fixed intervals, aliquots (5ml) were withdrawn and replaced with fresh dissolution media. The concentration of drug release at different time intervals was then determined by measuring the Absorbance using visible spectrophotometer at 475nm against blank. The studies were carried out in triplicate.

FTIR Studies [13]: FTIR Spectroscopy was performed on each at samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore drug polymer interactions were examine using the resulting spectra. The infrared spectra were obtained using a scale of wave numbers (cm^{-1}). The analysis were performed by using a thermo nicolet nexus 470 FTIR ESP. 3-5 mg of sample was added to approximately 100mg of KBr. The mixture was then ground to a fine powder using a mortar and pestle and transparent discs formed using a pellet press. The discs were placed in FTIR spectroscopy apparatus and spectra were collected. The range of the collected spectra was 4000-400cm^{-1} **(Figures 3, 4, 5, 6).**

Wettability Studies [14]: Pure drug approximately 1gm was placed in sintered glass funnel with the heap of cotton plug. The funnel was held in upright position in a beaker filled with the water level in the beaker just touched the cotton plug. The time required to raise the water through the drug for the colorings of water was recorded. Same procedure was followed for all solid dispersions.

Solubility Studies [15]: Pure drug (20mg), its physical mixture and solid dispersion with PEG 6000 under test was placed in a test tube containing 1ml distilled water. The samples were shaken at room temperature until saturated solution formed and the aliquots were filtered. The filtered samples were diluted suitably and assayed Spectrophotometrically at 475mm.

Angle of Repose [16]: To get an idea about flow ability properties of the solid dispersion, angle of repose for all the batches was determined, suitable for solid dosage form preparation.

RESULT AND DISCUSSION: The objective of the study was to develop and evaluate PEG solid dispersions of rifampicin. Four core:coat ratios namely 1:1, 1:2, 1:3 and 1:10 were used to prepare PEG solid dispersions by common solvent method **(Table 1).** As per **figures 1 and 2** reveals that the surface morphology of rifampicin and its binary systems was examined by SEM analysis. The rifampicin crystals appeared as fine needles with smooth surfaces, irregular shape and partially agglomerated in bundles. In solid dispersions, rifampicin particles were in almost amorphous form, which indicated a reduction in particle size. Paricle size is directly proportional to surface area and this effect was the drug release from solid dispersions.

Figures 3, 4, 5, 6 shows compatibility studies of rifampicin and the carriers were carried out by using FTIR spectrophotometer. In IR spectrum, shown differences between 3000-600cm^{-1} region and it indicates that no interaction between drug and polymers. **Table 2** shows the time required for rising water through capillary action to wet the drug was found to be range of 9-12 min. For all the solid dispersions which was significantly less when compared with 35 mins for pure drug and 32 mins for physical mixture.

The wetting time of SD1, SD2, SD3 and SD10 was found to be 21, 12, 10 and 9 mins respectively. Solubility of rifampicin in solid dispersions was more than the pure drug and physical mixture. Solubility of pure drug was found to be 2mg/ml where as for physical mixture was 50mg/ml. Solubility of rifampicin in SD1, SD2, SD3, SD10 was found to be 15, 25, 50, 225mg/ml. As the ratio of core:coat ratio increases, solubility also increase, this may be due to more soluble polymer nature of polymer and more size reduction and presence of amorphous nature of drug in solid dispersions. The drug content estimated in each 50mg of various solid dispersions [1:1,1:2,1:3 and 1:10] were found in the range of 4.3-26.82mg in methanol. **Table 3** and **figures 7, 8** shows *In-vitro* release studies were performed in pH 7.4 for 2 hrs.

The release rate of solid dispersions SD1,SD2,SD3, and SD10 in pH 7.4 were found to be 47.89%, 87.96%,97.80% and 100.0% respectively where as for pure drug and physical mixture were found to be 30.20% and 76.00% respectively. It indicates that increase in concentration of coat material (PEG) resulted in increase in the release rate.

TABLE 1: FORMULA

Code	Drug: Carrier Ratio	Method of Preparation
Physical mixture	1:10	Physical mixture
SD1	1:1	Solvent Evaporation method
SD2	1:2	
SD3	1:3	
SD10	1:10	

TABLE 2: ANGLE OF REPOSE AND SOLUBILITY, WETTABILITY, DRUG CONTENT DATA OF SOLID DISPERSIONS, PHYSICAL MIXTURE, PURE DRUG

Code	Angle of Repose (^{O})	Solubility (mins)	Wettability (mins)	Drug Content (mg)
Pure drug		2	35	8.00
Physical mixture	19.29	50	32	9.00
SD1	12.95	15	21	26.82
SD2	14.57	25	12	11.00
SD3	14.03	50	10	10.00
SD10	17.22	225	09	4.3

TABLE 3: *IN-VITRO* DRUG RELEASE STUDIES: CUM % OF DRUG RELEASE OF SD1, SD2, SD3, SD10, PURE DRUG, PHYSICAL MIXTURE

Time in mins	SD1	SD2	SD3	SD10	Pure drug	Physical mixture
0	0	0	0	0	0	0
10	32.15	44.99	32.15	38.18	6.12	25.47
20	35.11	49.99	35.11	45.01	7..41	31.00
30	36.38	56.39	36.38	47.80	8.35	34.60
40	37.78	63.48	37.78	69.44	10.56	39.20
50	39.22	68.35	39.22	90.19	12.41	41.85
60	39.84	74.59	39.84	92.19	14.28	45.01
70	41.12	77.39	41.12	95.00	15.08	48.17
80	41.83	78.60	41.83	97.01	15.70	53.11
90	42.38	81.01	42.38	98.20	16.15	57.69
100	43.66	85.05	43.66	99.25	16.23	62.67
110	45.77	86.31	45.77	99.50	17.76	68.85
120	47.89	87.96	47.89	100.0	19.19	76.04

SEM Photographs of Pure drug and SD10:

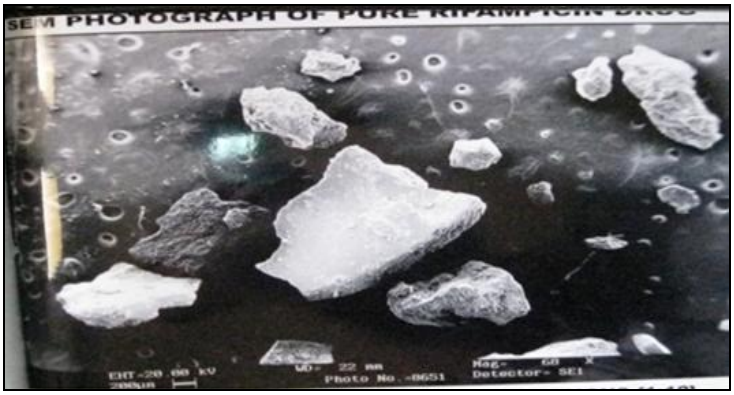


FIG. 1: SEM PHOTOGRAPH OF PURE RIFAMPICIN DRUG

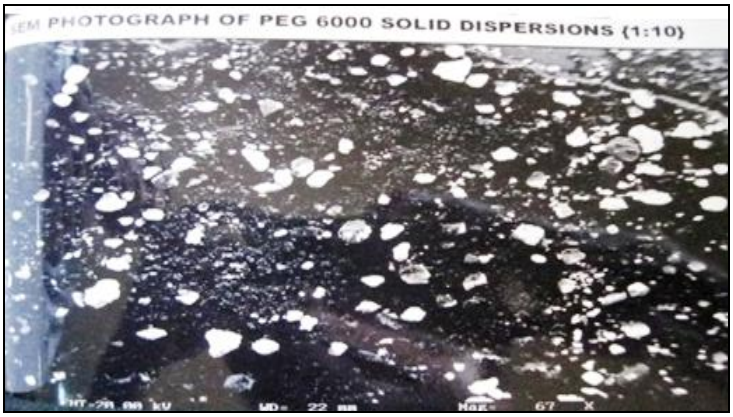


FIG. 2: SEM PHOTOGRAPH OF PEG 6000 SOLID DISPERSIONS (1:10)

IR Spectrums of Pure drug and Solid Dispersions:

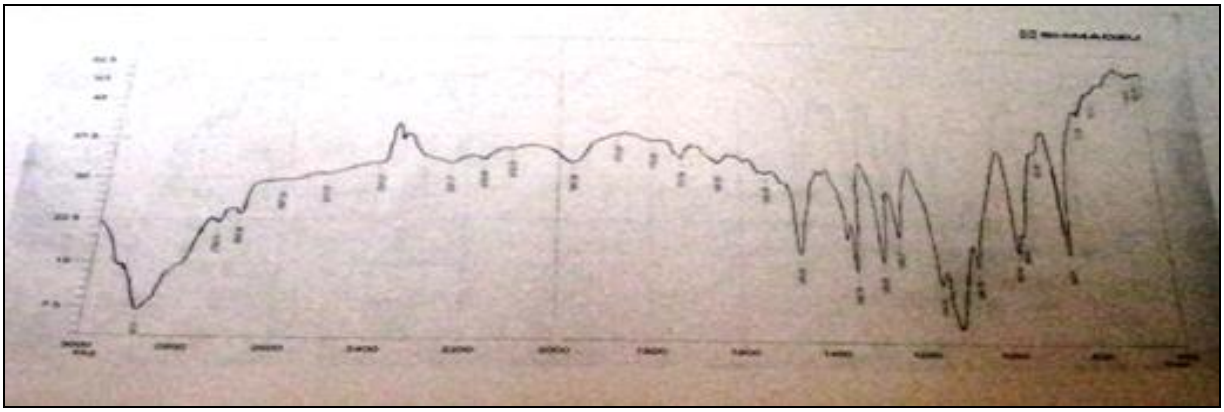


FIG. 3: IR SPECTRE OF PURE RIFAMPICIN DRUG

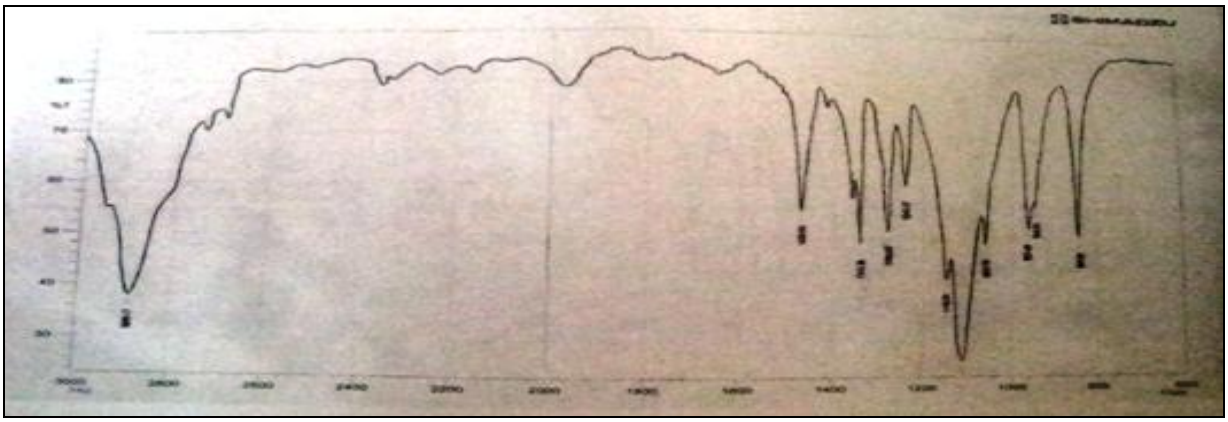


FIG. 4: IR SPECTRE OF PURE PEG 6000

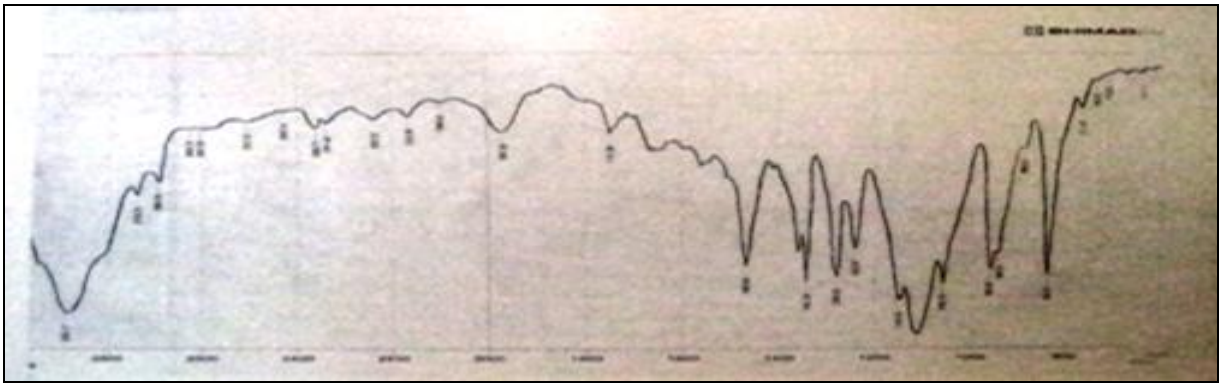


FIG. 5: IR SPECTRE OF PEG SOLID DISPERSION (SD10)

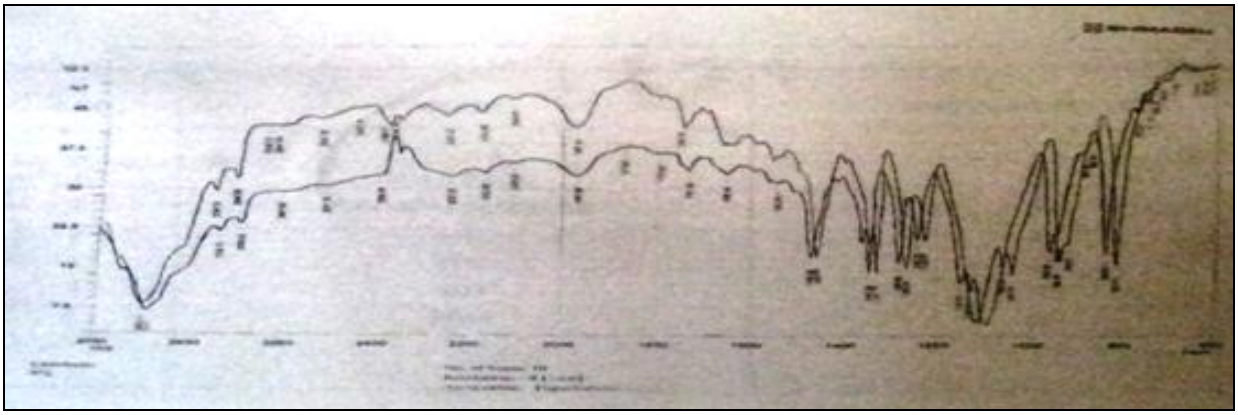


FIG. 6: OVERLAP IR SPECTRE OF PURE DRUG AND SOLID DISPERSIONS (SD10)

% Cumulative Release profiles of pure drug and Physical mixture, Solid dispersions:

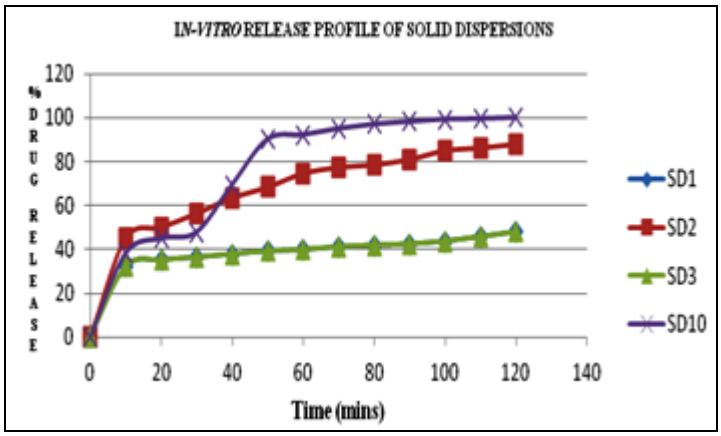


FIG. 7: COMPARISON OF % CUMULATIVE RELEASE PROFILE OF SD1, SD2, SD3, SD10

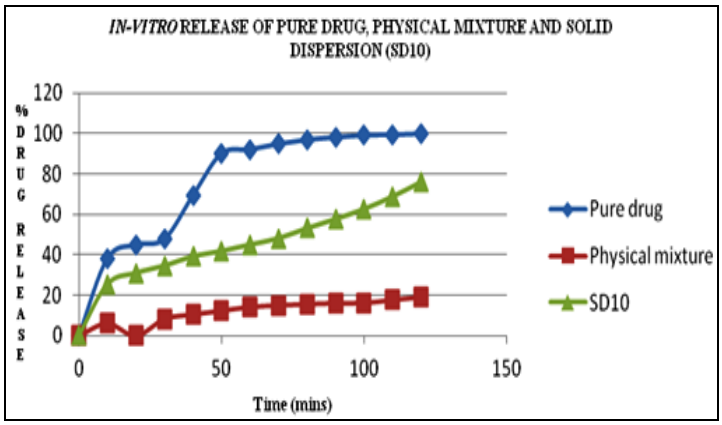


FIG. 8: COMPARISON OF % CUMULATIVE RELEASE PROFILE OF PURE DRUG, PHYSICAL MIXTURE AND SD10

CONCLUSION: Common solvent method of solid dispersions gave good batch yield and uniform drug content. Shape of solid dispersions was irregular with smooth surface and partially agglomerated in bundles, as indicated by SEM studies. FTIR Studies indicated no chemical interaction between drug and polymer. Wetting time was decreased with increased proportion of coat composition. Solubility of drug also increased with increased proportion of coat composition.

As the solid dispersions showed free flow property, so were considered suitable for tablet dosage form. *In-vitro* drug release showed fast and complete release over a period of 2 hrs in pH 7.4 release profile of solid dispersions(SD10) were compared with pure drug and physical mixture. Solid dispersions SD10 with core: coat ratio 1:10 was found better with respect to release profile, hence these are promising carriers for oral fast release of rifampicin. Studies have shown promising results these exits a scope for further *in-vivo* evaluation.

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REFERENCES:

1. Improving solubility & permeability in drug candidates conference: 23rd & 24th june 2005, pre-conference workshop:22nd june 2005, thistle marble, London, UK
2. Solubility. http://www.sciencebyjones.com/teaching%20menu.htm
3. Solubility from Wikipedia, the free encyclopedia, retrieved from http://en.wikipedia.org/wiki/splubility.
4. Adam M, Persky and Jeffrey A Hughes. Solutions and Solubility http:/www.cop.ufl.edu/safezone/prokai/ph5110/pha5110.htm
5. Pinnamaneni S, Das NG, Das SK: Formulation approaches for orally administered poorly soluble drugs. Pharmazie 2002; 57:291-300.
6. Rifampicin from Wikipedia, the free encyclopedia, retrieved from http://en.wikipedia.org/wiki/rifampicin.
7. Chiou WL, Riegelman S: Pharmaceutical applications of solid dispersion systems. J Pharm. Sci 1971; 60:1281-1302.
8. Ambike AA, Mahadik KR, Paradkar A: Stability study of amorphous valdecoxib. Int J. Pharm 2004; 282:151-162.
9. Paradkar A, Ambike AA, Jadhav BK, Mahadik KR: Characterization of curcumin-PVP solid dispersion obtained by spray drying. Int J Pharm 2004; 271:281-286.
10. Doshi DH, Ravis WR, Betageri GV: Carbamazepine and polyethylene glycol solid dispersion preparation, *in-vitro* dissolution and characterization. Drug Dey Ind pharm 1967; 23:1167-1176.
11. Alazaar N, Ghebremeskel, Chandra vemavarapu, Mayur lodaya: Use of surfactants as plaasticizers in preparing solid dispersions of poorly soluble APL: selection of polymer-surfactant combinations using solubility parameters and testing the processability. International journal of Pharmaceutics 2007; 328:119-129.
12. Geroge Z Papageoriou et al: Effect of physical state and poetical size distribution on dig solution enhancement of Nimodipine/PEG solid dispersions prepared by melt mixing and solvent evaporation. AAPS Journal 2006; 8(4):E623-E631.
13. David L, Tomasko et al: Analysis is of pharmaceutical/polymer solid dispersions produce by supercritical carbon dioxide-assisted techniques. 2005.
14. Yogesh Rane et al: Effect by hydrophilic Swellable polymers on Dissoltions enhancement of carbamazepine Solid dispersions studied using reponse surface methodology. Aaps pharmasci Tech 2007; (2):1-18.
15. Sengodam GVK, Dina NM: Preparation and Evaluation of Solid dispersion of meloxicam with skimmed milk. The pharmaceutical society of Japan 2006; 126(2):93-97.
16. Subrahmanyam CVS: Micrometrics. Vallabh Prakashan Publications, New Delhi, Edition 1, 1998:159.