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RESEARCH ARTICLE

Formulation and Evaluation of Extended Release Solid Dispersions Conatining Simvastatin

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ABSTRACT

The purpose of this research was to formulate and characterize solid dispersion (SD) of Simvastatin using Polyethylene glycol 4000 as the hydrophilic carrier and Methocel K15M as the release retardant by the solvent evaporation and co-grinding method. The influence of drug polymer ratio on drug release was studied by dissolution testing. Characterization was performed by Fourier Transform Infrared Spectroscopy (FTIR), and Ultraviolet Spectroscopy. Release data were examined kinetically. SD with 1:2 and 1:3 ratio of drug to polymer obtained by solvent evaporation and co-grinding were selected as the best candidates suitable for prolonged-release oral dosage form of Simvastatin.

KEYWORDS: Co-grinding, Simvastatin, Methocel, Solid dispersion, Solvent evaporation.

INTRODUCTION

Simvastatin (SIM), a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, which catalyzes the reduction of HMG CoA to mevalonate. Thus, Simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, Simvastatin is metabolized to its β-dihydroxy acid form (Simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability. [1] Most of the available statins, including Simvastatin, were developed as immediate release (IR) formulations. Adverse reactions commonly reported with these formulations include upper respiratory tract infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%). Hepatotoxicity and myotoxicity are the most serious adverse events associated with the statins, with higher concentrations associated with a higher incidence of adverse events. It has been hypothesized that the CR formulations would avoid the saturation of oxidative biotransformation without sudden elevation of systemic drug concentrations and thus would reduce the side effects.[2]

Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semisynthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released the drug at a constant rate for a desired time period.

Solid dispersion (SD), in which compounds are dispersed into water-soluble carriers, has been generally used to improve the dissolution properties and the bioavailability of drugs those are poorly soluble in water. SD has also been applied for the controlled release of drugs. Previous reports have shown that by using Solid dispersions containing a polymer blend, such as hydroxypropylcellulose(HPMC) and ethylcellulose, it is possible to precisely control the rate of release of an extremely water-soluble drug, such as oxprenolol hydrochloride. SDs of methylcellulose and carboxyvinylpolymer for phenacetin and Eudragit for diclofenac sodium. These studies have shown that there is a linear relationship between the rate of release of the water-insoluble drug and its interaction with the polymer [3]

A wide array of polymers has been employed as drug-retarding agents, each of which presents a different approach to the matrix concept. Polymers that primarily form insoluble or skeleton matrices are considered as the first category of retarding materials. The second class represents hydrophobic and water-insoluble materials, which are potentially erodible, and the third group exhibits hydrophilic properties. There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation and swelling followed by diffusion. The release of drug from the matrix

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depends on the nature of the polymer. Methocel K15 M is a hydrophilic polymer that becomes hydrated, swollen and facilitates diffusion of the drug. In the present study, an attempt has been made to formulate Simvastatin as SR SD with the addition of release-retarding polymer methocel K15M in different ratios. The effects of polymer loading on drug release were recorded and the release kinetics was evaluated.

MATERIALS AND METHODS

Simvastatin was obtained as a gift sample from Wockhardt ltd., (Aurangabad, India) and hydroxypropylmethylcellulose (Methocel K15M) was obtained from Colorcon Asia Pvt. Ltd. (Mumbai, India). All other chemicals and solvents were of reagent grade.

PREPARATION OF PHYSICAL MIXTURES

Physical mixtures of Simvastatin and methocel in powder form were mixed in mortar and passed through sieve no. 60. The physical mixture was prepared in the ratio of 1:1.

SOLID DISPERSIONS PREPARED BY THE SOLVENT EVAPORATION METHOD

Dissolved the weighed amount of Simvastatin in minimum quantity of ethanol. HPMC K 15M and hydrophilic carrier PEG 4000 was suspended. The suspension was continuously stirred at 100 rpm using magnetic stirrer at room temperature until all the solvent evaporated. The solid dispersions were dried in an oven at 40^{o}C, sieved through 60# and further were stored in a desiccator in a screw-capped glass vial until use.[4]

SOLID DISPERSIONS PREPARED BY THE CO-GRINDING TECHNIQUE:

Weighed amount of Simvastatin was triturated with sufficient quantity of ethanol till it dissolved. Then added, PEG 4000 and HPMC K 15M and further triturated. The solid dispersions were dried in an oven at 40^{o}C, sieved through 60# and further were stored in a desiccator in a screw-capped glass vial until use.[7]

EVALUATION AND CHARACTERIZATION OF SOLID DISPERSION (DRUG CONTENT)

Solid dispersions equivalent to 20 mg of Simvastatin were weighed accurately and dissolved in 10 ml of methanol. The stock solutions were diluted in distilled water and analyzed by UV-vis spectrometry at 238 nm.[5]

SATURATION SOLUBILITY STUDIES

Saturation solubility was determined using shake flask method. Solid dispersions in excess quantity were placed in separate stoppered flasks containing 10 ml distilled water. The samples were placed in an orbital shaker at 37^{o}C and 100 rpm until equilibrium was achieved (24 hrs). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm.[5]

FTIR ANALYSIS

The IR spectrum of each drug was recorded using Perkin Elmer- FTIR Spectrometer Spectrum RX-I. About 5mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted using a hydraulic press at a pressure of about 100- 150 kg cm^{-2} for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 625 cm-1. The resultant spectra were compared with standard spectra in the Indian Pharmacopoeia.[6]

DISSOLUTION STUDY

In-vitro drug release studies of the extended release solid dispersion were conducted for a period of 12 Hr using USP XXШ type two apparatus (Lab India Disso 2000) at 37 ± 0.5℃ and 50 rpm speed. Samples equivalent to 20 mg of Simvastatin were filled in size 0 hard gelatin capsules and placed in the basket. Media used was 900 ml of 0.01 M phosphate buffer pH 7.0 with 0.5% sodium lauryl sulfate. At specific hour interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the sink conditions. After filtration and appropriate dilution, the samples were analyzed by a UV spectrophotometer (Shimadzu UV-250 1PC double beam spectrometer) at 238 nm. The total content of Simvastatin in the sample was calculated using the appropriate calibration Curve constructed from reference standards.[6]

RELEASE KINETICS FORM MATRIX BASED CONTROLLED-RELEASE DOSAGE FORMS

The *in vitro* release data of the stability batches were analyzed and various kinetic models were used to describe the release kinetics. The following plots were made: *cumulative % drug release vs. time* (zero order kinetic model); *log cumulative of % drug remaining vs. time* (first order kinetic model); cumulative *% drug release vs. square root of time* (Higuchi model) *log cumulative % drug release vs. log time* (Korsmeyer Peppas model) and *cube root of drug % remaining in matrix vs. time* (Hixson-Crowell cube root law).[7]

Parameters	Specification
Apparatus	Basket, Type I (USP)
Speed	50 rpm
Dissolution Medium	Phosphate Buffer pH 7.0
Volume of Dissolution Medium	900 ml
Sampling Time	0, 1, 2, 4, 6, 8, 10, 12 hrs
Temperature	37 ± 0.5 º C

Table 1: Dissolution study protocol

RESULTS

DRUG CONTENT AND SOLUBILITY

Table 2 summarizes the actual composition and saturation solubility data along with abbreviations used for the solid dispersions. Drug content for all the solid dispersion formulations were in the range of 90.00-110.0% acceptable according to Indian Pharmacopoeial standards. [6]

Trial	Formulation code	Drug content (%)	Saturation Solubility (37^0C) (µg/ml)
Physical mixture (1:1)	PM	98.50	71.35
Solvent evaporation (1:1)	F1	98.33	70
Solvent evaporation (1:2)	F2	98.67	72.35
Solvent evaporation (1:3)	F3	98.20	71.5
Co-grinding technique (1:1)	F4	99.35	74.50
Co-grinding technique (1:2)	F5	98.70	73.25
Co-grinding technique (1:3)	F6	98.23	74.50

Table 2: Drug content and solubility data.

FTIR

FTIR spectroscopy was used to study the possible interactions between Simvastatin and the polymer in the SD. There is no significant difference in the FTIR spectra of pure drug, physical mixture, and SD (Figure1.1). All major peaks of Simvastatin were observed at wavenumbers 3553 cm^{-1} (free O–H stretching vibrations); 3011, 2959, and 2872 cm^{-1} (C–H stretching vibrations); and 1714 cm^{-1} (stretching vibration of ester and lactone carbonyl functional groups) were retained in physical mixtures and SD, which clearly indicate that no interaction exists between pure drug and polymer in SD.[6]

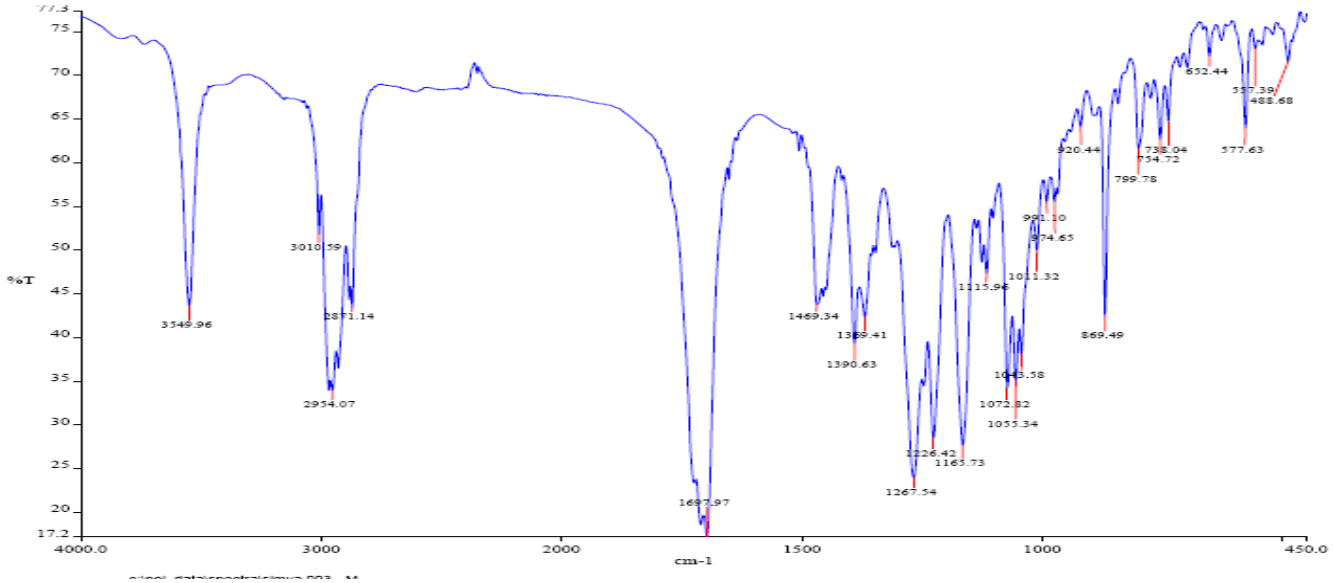

Figure 1.1: IR spectrum of Simvastatin

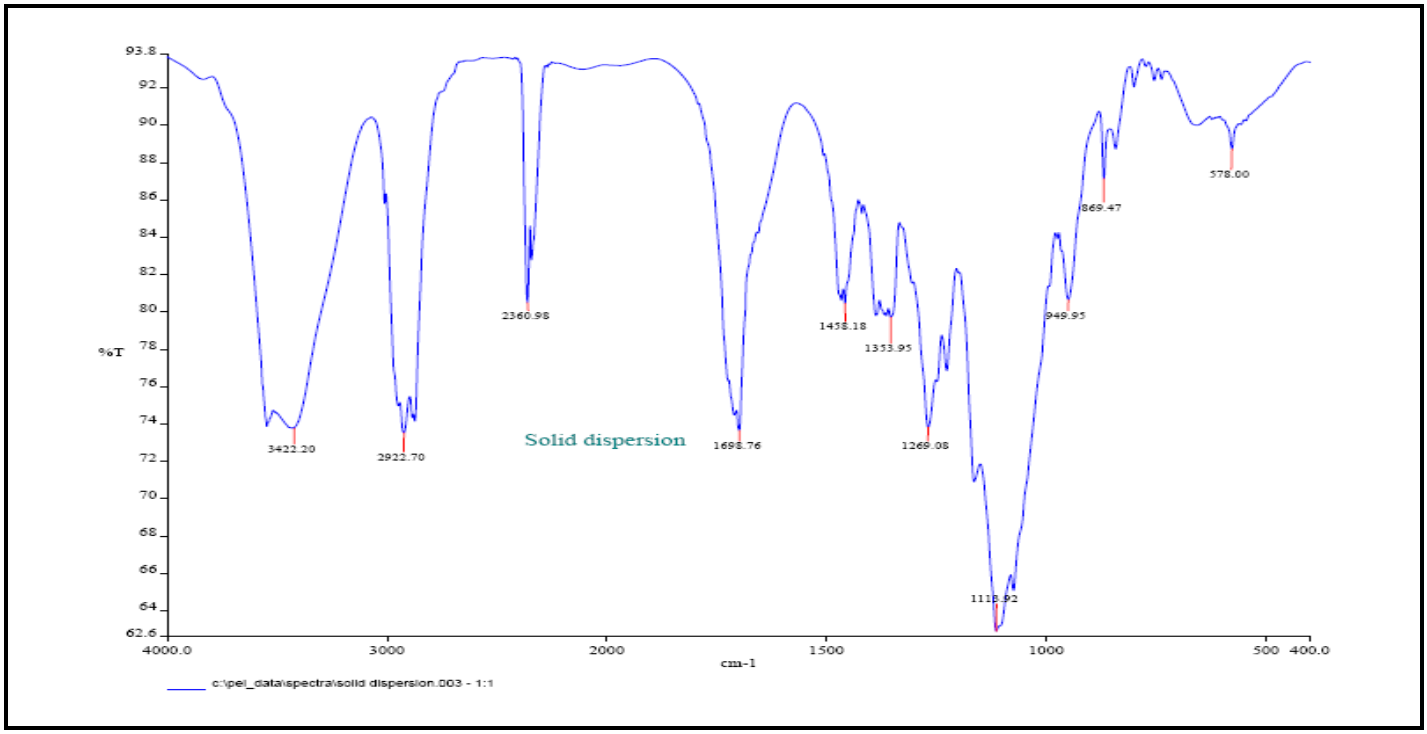

Figure 1.2: IR spectrum of Solid dispersion by Solvent evaporation technique

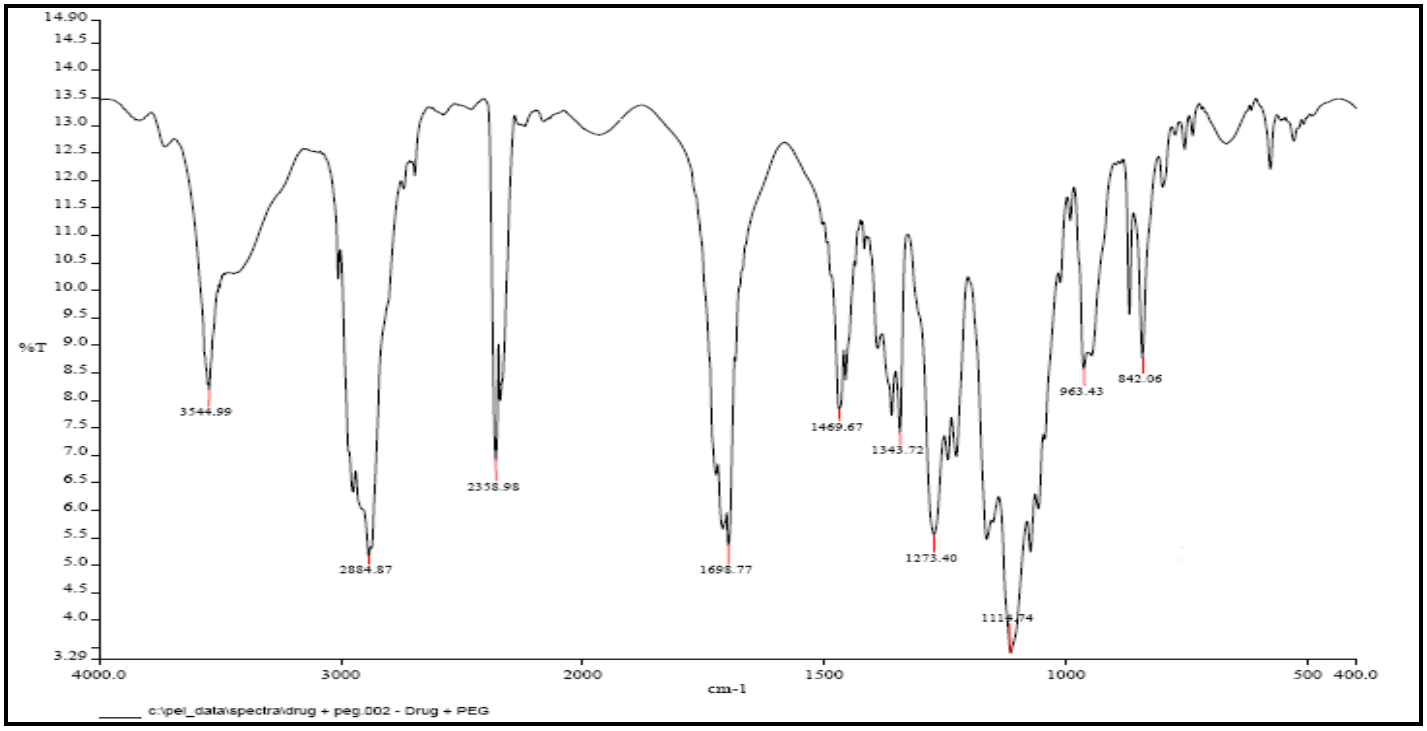

Figure 1.3: IR spectrum of solid dispersion by Co-grinding Technique

DISSOLUTION STUDY

The dissolution profiles of Simvastatin SDs along with physical mixture are shown in Figures for solvent evaporation and co-grinding, respectively. The dissolution from the solid dispersion showed very slight initial slowing down of the drug dissolution rate due to the presence of the hydrophilic HPMC, which reduces the drug wettability.

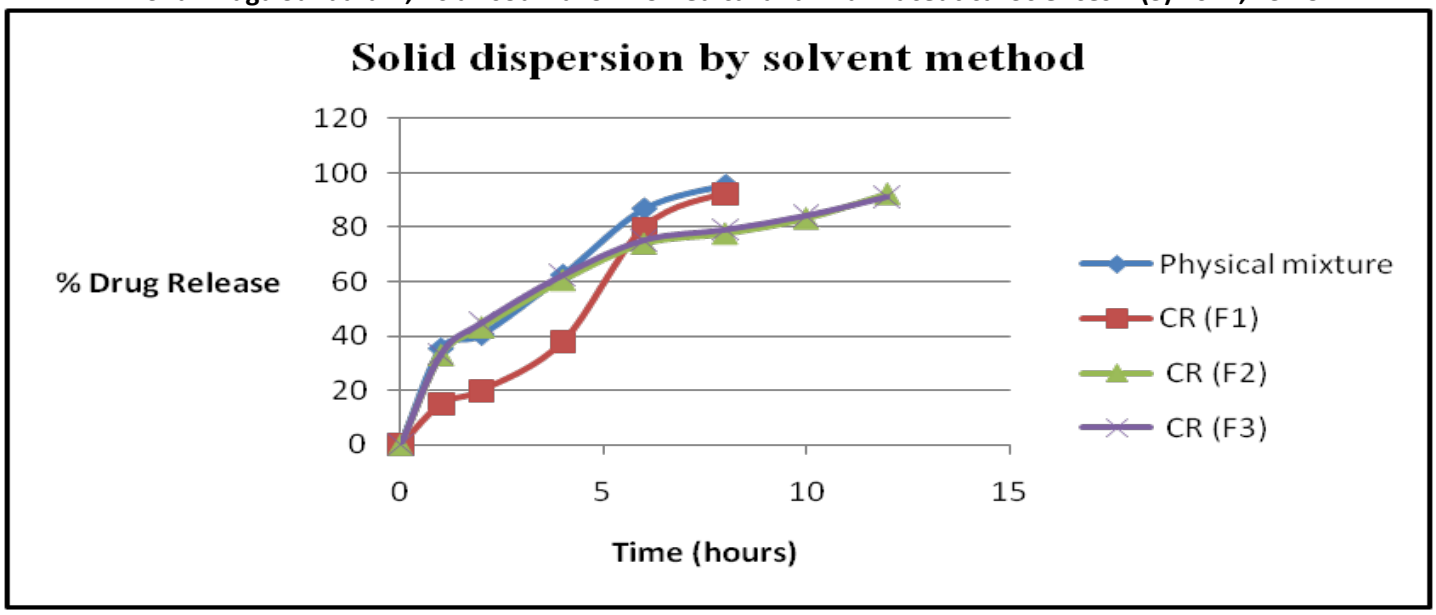

Figure 1.4: Dissolution study of solid dispersion by solvent method

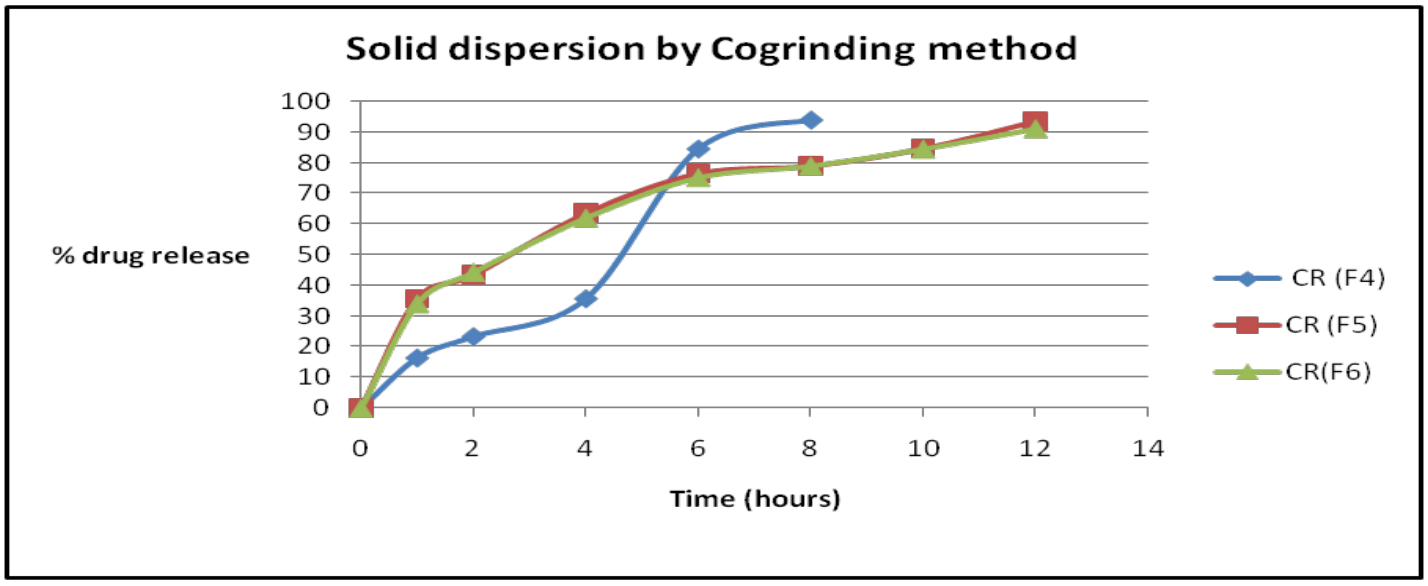

Figure 1.5: Dissolution study of solid dispersion by co-grinding technique

RELEASE EXPERIMENTS

The release data of selected SDs were examined according to the zero-order, first-order and Higuchi's square root of time mathematical models, Hixson and Crowell powder dissolution method and Korsmeyer and Peppas model and the release exponent n was calculated. Table shows the data for kinetics of SDs.

Model	R^2 value					
	F1	F2	F3	F4	F5	F6
Zero order	0.972	0.58	0.83	0.95	0.83	0.837
First order	0.908	0.98	0.98	0.89	0.96	0.98
Higuchi	0.93	0.98	0.98	0.86	0.97	0.98
Hixson-Crowell	0.801	0.506	0.50	0.77	0.50	0.50
Korsmeyer-peppas	0.947	0.990	0.99	0.92	0.984	0.991

Table 3: Kinetics data of solid dispersions

It can be observed that the Higuchi equation was the most suitable mathematical model for describing experimental data only for F2, F3 and F6 containing drug to polymer in a 1:2 and 1:3 ratio, indicating that diffusion through the matrix was the main factor in controlling the drug release rate from SDs. Whereas again in case of F2, F3, F6, the Korsmeyer-Peppas equation was most suitable with R^2 value of 0.9978 and that of first-order equation was 0.9832, indicating that the drug-release pattern is followed by both the equations. Thus the *in vitro* release pattern of the SDs was analyzed by fitting the dissolution data into various kinetic models. It was observed that the R^2 value was higher when fitted to Korsmeyer-Peppas equation as compared to zero-order equation, which indicated Peppas as the best fitting kinetic model for F2, F3 and F6.

DISCUSSION

IN VITRO RELEASE STUDY

Drug release was fast from F1 and F4 SDs, with about 93% drug released within 7 hrs, because it underwent erosion before complete swelling could take place. The overall drug release is affected by the rate of water uptake and the diffusion rate of the drug through the swollen gel. High polymer content results in a greater amount of gel being formed. This gel increases the diffusional path length of the drug. Its viscous nature also affects the diffusion coefficient of the drug. As a result, a reduction in drug release rate is obtained. On increasing the quantity of HPMC in 1:2 and 1:3 ratio of drug, prolonged release of the drug was achieved, giving drug release of 95.31 and 92.63%, respectively, after 10 hrs and in the desired pattern. As the ratio of drug to polymer increases, there is a significant decrease in the drug release from the SDs, reaching 90% of dissolved drug after about 10 hrs for F2 and F3. As the quantity of polymer increases further, there is also decrease in the amount of drug release from SD, giving an extended release up to 10 h for F5 and F6. The slow drug-release form SD, namely F5 and F6, can be attributed to the low permeability of the polymer, which posed a significant hindrance to fluid penetration and passive drug diffusion. The results indicate that there is reduction in drug release as there is increase in the amount of HPMC.

KINETIC STUDIES

The mechanism of drug release from hydrophilic SD after ingestion is complex, but it is based on diffusion of the drug through, and erosion of, the outer hydrated polymer on the surface of the SD. Typically, when the dispersion is exposed to an aqueous solution or gastrointestinal fluids, the surface of the dispersion is wetted and the polymer hydrates to form a gel layer around the drug. This leads to relaxation and swelling of the polymer, which also contributes to the mechanism of drug release. The core of the dispersion remains essentially dry at this stage. In the case of highly soluble drugs like metformin, this phenomenon may lead to an initial burst release due to the presence of the drug on the surface of the dispersion, which is evident by the dissolution data. The gel layer grows with time as more water permeates into the core of the dispersion, thereby increasing the thickness of the gel layer and providing a diffusion barrier to drug release. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, thereby leading to disentanglement and erosion of the surface of the dispersion. Water continues to penetrate toward the core of the dispersion, through the gel layer, until it has been completely eroded.

CONCLUSION

The proposed strategy of simultaneously exploiting the combination of the drug with a hydrophilic polymer such as methocel K15M, hydrophilic carrier PEG 4000 and its SD was effective in adequately modulating the drug-release rate. Release experiments demonstrate that the extended release effects can be obtained by simply varying the relative amounts of the polymer in the dispersion. The actual effectiveness of SDs as extended release dosage forms is strongly dependent on the preparation technique used for obtaining SD. SDs prepared by solvent evaporation using methocel K15M were capable of prolonging the release of Simvastatin for 10 h at 80% concentration and by the cogrinding method at 83% concentration of the polymer. The mechanism of drug release was observed to follow the Korsemeyer-Peppas model for F2, F3, F6 and the Higuchi matrix model for F2, F3, and F6 SDs.

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