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Original Article

Comparative study of different solubility enhancement techniques on dissolution rate of zaltoprofen

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ABSTRACT

The aim of present work to prepare solid dispersion of zaltoprofen, a water insoluble drug, with β-cyclodextrin in order to improve the solubility and dissolution rate of drug. The solid dispersions of zaltoprofen-β-CD prepared by different methods were characterized by Differential Scanning calorimetry (DSC), Powder X-ray Diffraction (XRD), Fourier-transform infrared spectroscopy, solubility and dissolution studies. Identification of polymorphism done by X-ray diffraction and for thermo dynamic properties using DSC. The solubility of all the solid dispersions showed improvement compare to pure drug. The drug release profile was carried out in phosphate buffer 6.8 pH using USP type II paddle dissolution apparatus. From the studies, it was found that the kneading method shows the better enhancement of dissolution in compare to physical mixture, solvent evaporation, fusion method and microwave induced radiation.

Key Words: Zaltoprofen, β-CD, Solid dispersion, solubility, *in-vitro* drug release

INTRODUCTION

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 dose in order to reach therapeutic plasma concentrations after oral administration.[1]

Zaltoprofen is a propionic derivative of non-steroidal anti-inflammatory drugs. It has powerful inhibitory effect on acute and chronic inflammation with less adverse reactions on the gastrointestinal tract than other NSAIDs. Zaltoprofen exerts anti-inflammatory actions and analgesic effects by inhibiting prostaglandin synthesis and through a peripheral mechanism by inhibition of bradykinin B2 receptor-mediated bradykinik responses in primary afferent neurons. Zaltoprofen was already used in the treatment of rheumatoid arthritis and osteoarthritis as well as to relieve inflammation and pain after surgery, injury and tooth extraction.[2-6]

Cyclodextrins are crystalline, cyclic oligosaccharides with a bucket-like structure having a hydrophobic internal cavity and a hydrophilic exterior cavity that allows the configuration of inclusion complexes, in which lipophilic compounds are non-covalently bound within the cavity. Cyclodextrin have been employed in the pharmaceutical industry to increase the aqueous solubility and stability of drugs and that have been used in both parenteral and oral drug delivery systems.[7-10]

The objective of the present investigation is to increase the solubility and dissolution rate of zaltoprofen by the complexation with β-cyclodextrin using physical mixing, kneading, solvent evaporation, fusion and microwave induced radiation.

MATERIALS AND METHODS

Materials: Zaltoprofen was purchased from Honda suppliers, Mumbai. β-cyclodextrin was obtained from astron Laboratory,Ahmedabad.

Methods:
Complexation with cyclodextrin has been reported to enhance the solubility, dissolution rate and bioavailability of poorly water soluble drugs. Among the cyclodextrin, β-cyclodextrin is the most widely studied compound for drug complexation. To improve solubility and dissolution rate of zaltoprofen via complexation with β-CD, different

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ratios(1:1, 1:2, 1:3) were prepared using physical mixing, kneading, solvent evaporation, fusion and microwave induced radiation method.

A) **Physical Mixture:** Physical mixtures of zaltoprofen with β-cyclodextrin were prepared by mixing them in different ratios from 1:1 to 1:3 w/w simply using a mortar and pestle.
B) **Kneading Method:** The zaltoprofen and β-cyclodextrins complexes (1:1, 1:2 and 1:3) were prepared by kneading technique. In this method required amount of drug and β-cyclodextrin were taken and transferred to a mortar pestle. The mixture was size reduced by continuous stirring with pestle. Acetone was added to the above physical mixture and continuously stirred until the slurry mass was formed. Slurry mass collected and dried in a hot air oven for 60 min at 50ºC, dried mass was collected and further dried in desiccators for 24 hrs to remove all the excess residual solvents. The dried mass was collected and passed through 60# mesh and store.
C) **Fusion Method:** The required quantity of β-cyclodextrin was taken in china dish and it was heated in heating mentle. The carrier is heated to melt it and then required quantity of drug was incorporated in molten carrier. Then it was cooled and solidified by placed over ice. Finally solid mas was crushed, pulverized and pass through the sieve number 60.
D) **Solvent Evaporation Method:** Zaltoprofen and β-cyclodextrins complexes with different ratios were prepared by solvent evaporation method. In this method required quantity of β-cyclodextrins and zaltoprofen was dissolved in sufficient amount of methanol:acetone (1:1) in china dish. The solvent from the solution was removed at 45ºC with continuous stirring to obtained dry mass. Dried mass was pulverized through 60 # mess and stored.
E) **Microwave Induced Radiation Method:** The required quantity of drug and β-cyclodextrin of different ratios were taken into a glass beaker and subjected to microwaves for 5 min at the chosen power of 600 W in a domestic microwave oven. Only one beaker at a point in time was placed inside the microwave oven in an accurate place. Solid dispersions were then grounded in glass mortar and then passed through 60 mesh sieve to get uniform particle size.

EVALUATION PARAMETERS:

SOLUBILITY STUDY: An excess amount of pure zaltoprofen and the solid dispersions prepared were placed in contact with phosphate buffer pH 6.8. The samples were shaken for 24 hrs at room temperature in a orbital shaker. The supernatant was filtered through a membrane filter and the filtrate was suitably diluted and analyzed on UV-Visible Spectrometer at 243.5nm.

FTIR SPECTROSCOPY: Fourier transform infrared spectra of pure zaltoprofen and all the solid dispersions were obtained using an FTIR spectrometer (shimadzu corp., japan) equipped with a pyroelectric detector. The spectra were measured over the range 4000-400 cm^{-1} with an instrument resolution of 4 cm^{-1}.

DIFFERENT SCANNING CALORIMETRY: DSC was performed on pure zaltoprofen and all the formulation prepared by solid different methods using a differential scanning calorimeter. Samples (2-4mg) were sealed in aluminium pans. DSC thermograms were recorded from 50ºC to 300ºC at a heating rate of 20ºC/min in an air atmosphere.

X-RAY POWDER DIFFRACTOMETRY: To determine the powder characteristics, X-ray powder diffraction studies of solid dispersions were performed. The scanning rate employed was 2^o min^{-1} over 10 to 30^o diffraction angle (2θ) range. It was carried out at SICART, vidhyanagar.

DRUG CONTENT STUDY: The equivalent to 100 mg of solid dispersion was accurately weighed and transferred to 100 ml volumetric flask and dissolved with small quantity of methanol, then volume was adjusted with phosphate buffer and filtered. From this 1 ml was taken into 100 ml volumetric flask and the volume was adjusted with phosphate buffer. The absorbance of the solution was measured at 243.5 nm using appropriate blank. The drug content of zaltoprofen was calculated using calibration curve.

DISSOLUTION STUDY: The dissolution studies of pure zaltoprofen and all the solid dispersions were performed using the USP Type II paddle method (Dissolution test apparatus, electrolab Mumbai) with a stirring speed of 50 rpm in a 900 ml phosphate buffer solution having pH 6.8 as a dissolution medium. Samples containg 80 mg of zaltoprofen were spread onto the surface of dissolution medium at 37±0.5ºC. At appropriate time intervals, aliquots of 5 ml were withdrawn and measured spectrophotometrically by using UV-VIS spectrophotometer at 243.5nm. Experiments were carried out in triplicate.

RESULT AND DISCUSSION

SOLUBILITY STUDY: The effect of complexation with β-CD on solubility of zaltoprofen can be explained in terms of the

reduction in the crystallinity of the drug caused by the complexation and inclusion into the hydrophobic cavity of the β-cyclodextrin. Solubility of pure drug was found to be 0.0099 mg/ml. The maximum aqueous solubility was observed in K1 formulation among all formulation which was prepared by kneading method. By seeing results, it shows that drug:carrier (1:1) ratio is good to enhance solubility and dissolution rate. Results are shown in table 1.

DRUG CONTENT STUDY: Drug-carrier mixture of zaltoprofen with β-cyclodextrin were prepared by mphysical mixture, kneading method, solvent evaporation, fusion and microwave induced radiation method. The percentage of drug content of all the mixtures varied from 94.60±1.70% to 98.55±0.58% as shown in table. This result indicates that there was uniform distribution of the drug throughout the prepared solid dispersion. It shows that formulations prepared by kneading method has higher drug content. The results are shown in table 2.

FTIR STUDY: In order to further study whether zaltoprofen undergoes a polymorphic change during the preparation of the complex by solid dispersion and to test for possible intermolecular interactions between zaltoprofen and β-CD, FTIR was used. It was found that there is no interaction between drug and carrier. The results are shown in figure 1-3.

DSC STUDY: DSC is a very useful tool in the investigation of thermal properties of cyclodextrin complexes and can supply both quantitative and qualitative information about the physicochemical state of the drug inside the cyclodextrin complexes. In general, complexation results in the absence of endothermic peak or shifting to different temperature, indicating a change in the crystal lattice, melting, boiling or sublimation points. DSC thermograms of pure drug displayed endothermic peak at 138.96^{o} C corresponding to its melting point. The endothermic peak of all the solid dispersions were slightly shifted to 137.97^{o}C to 136.95^{o}C. The endothermic peak at 148.64^{o}C due to the formation of complexation with β-CD. This can be considered as complex formation between zaltoprofen and beta cyclodextrin, resulting in improved aqueous solubility and chemical stability. The DSC thermogram of drug and solid dispersion prepared by physical mixture and kneading method shown in figure 4-6.

XRD STUDY: XRD was carried out to identify the polymorphism changes during complex formation. By XRD study it was confirmed that there is no change in polymorphism of drug during the formation of complex. The XRD diffractogram of drug and solid dispersions prepared by physical mixture and kneading method shown in figure 7-9.

DISSOLUTION STUDY: The dissolution rate of pure drug and solid dispersion prepared by different methods were examined in phosphate buffer Ph6.8. From result it can be noted that dissolution rate of pure drug was 56.63% drug release during 60 min of dissolution. Whereas prepared solid dispersions of drug remarkably improve the dissolution rate of zaltoprofen.

The pure drug zaltoprofen showed 56.63 % release in 60 min. whereas physical mixture of zaltoprofen and β-cyclodextrin, formulation P1, P2 and P3 showed 91.98%, 90.37% and 88.31% respectively. Solid dispersion prepared by kneading method, formulation K1, K2 and K3 showed 92.12%, 90.69% and 89.97% respectively.

Solid dispersion prepared by solvent evaporation method, formulation S1, S2 and S2 showed 79.53%, 76.43% and 75.62% respectively.

Solid dispersion prepared by fusion method, formulation F1, F2 and F3 showed 75.38%, 76.78% and 74.54% respectively.

Solid dispersion prepared by microwave induced radiation method, formulation M1, M2 and M3 showed 73.62%, 75.15% and 71.78 respectively. The % drug release of all solid dispersions are shown in figure 10-14.

CONCLUSION: The various methods like physical mixing, kneading, solvent evaporation, fusion and microwave induced radiation using beta cyclodextrin were employed to enhance solubility and dissolution rate. The evaluated parameter showed decrease in crystilinity of drug. The solid dispersion prepared by kneading method showed a most effective method showing better solubility and dissolution rate compared to other methods.

Formulation code	Solubility
P1	0.97 mg/ml
P2	0.81 mg/ml
P3	0.76 mg/ml
K1	0.98 mg/ml
K2	0.86 mg/ml
K3	0.82 mg/ml
S1	0.56 mg/ml
S2	0.44 mg/ml
S3	0.39 mg/ml
F1	0.35 mg/ml
F2	0.36 mg/ml
F3	0.29 mg/ml
M1	0.31 mg/ml
M2	0.34 mg/ml
M3	0.28 mg/ml

Table 1. Solubility of prepsred solid dispersions.

Formulation code	Drug content%
P1	97.46±0.96
P2	97.44±3.22
P3	96.60±1.80
K1	96.54±0.58
K2	98.24±1.41
K3	98.55±0.58
S1	96.53±1.28
S2	97.87±1.35
S3	96.63±0.60
F1	97.86±0.39
F2	97.36±1.32
F3	96.65±2.05
M1	92.48±1.12
M2	94.19±0.79
M3	92.65±1.34

Table 2. Percentage drug content of prepared solid dipersiopns.

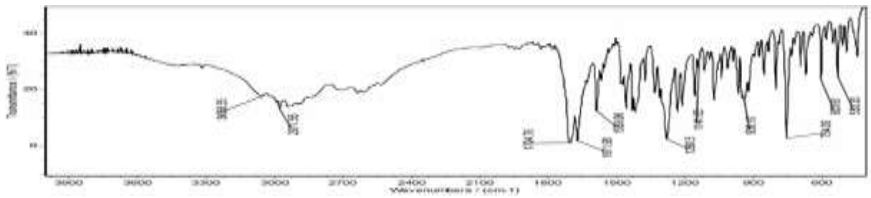

Figure 1. FTIR spectra of pure zaltoprofen.

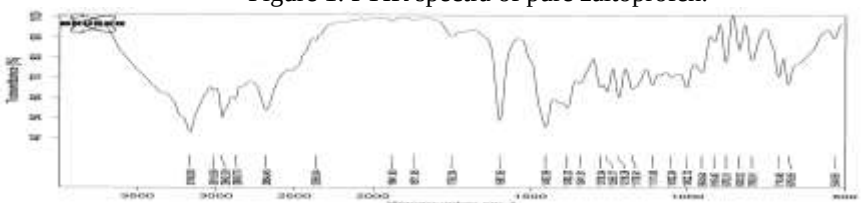

Figure 2. FTIR spectra of solid dispersion of zaltoprofen with β-cyclodextrin by physical mixture.

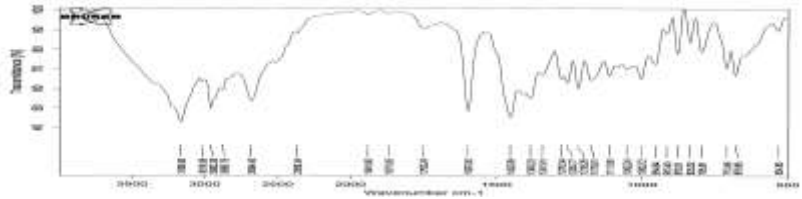

Figure 3. FTIR spectra of solid dispersion of zaltoprofen with β-cyclodextrin prepared by kneading method

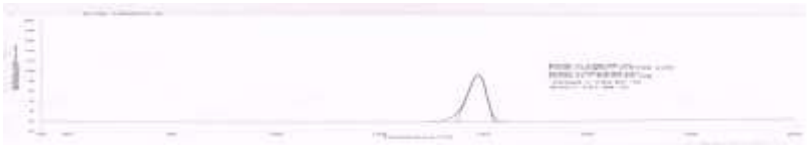

Figure 4. DSC thermogram of pure zaltoprofen

Figure 5. DSC thermogram of solid dispersion of zaltoprofen with β-cyclodextrin by physical mixture.

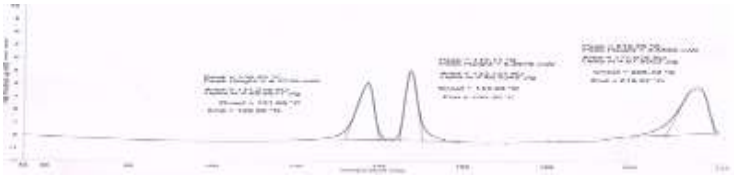

Figure 6. DSC thermogram of solid dispersion of zaltoprofen with β-cyclodextrin by kneading method.

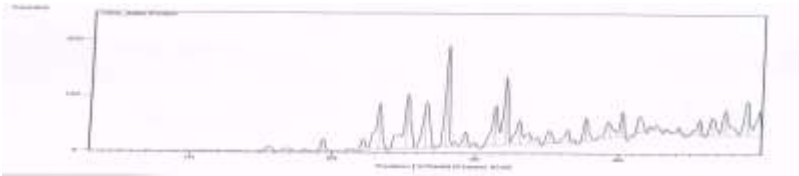

Figure 7. XRD diffractogram of pure zaltoprofen.

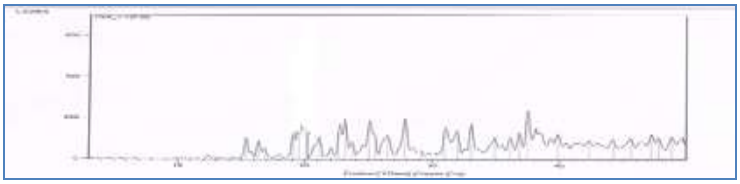

Figure 8. XRD differactrogram of solid dispersion of zaltoprofen with β-cyclodextrin prepared by physical mixture.

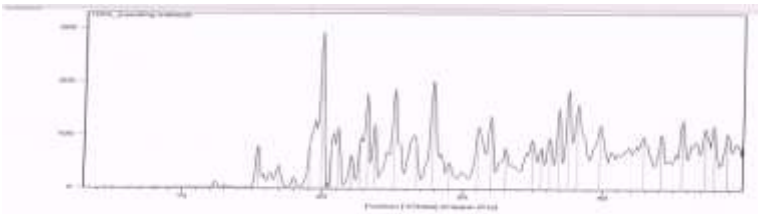

Figure 9. XRD differactogram of solid dispersion of zaltoprofen with β-cyclodextrin prepared by kneading method.

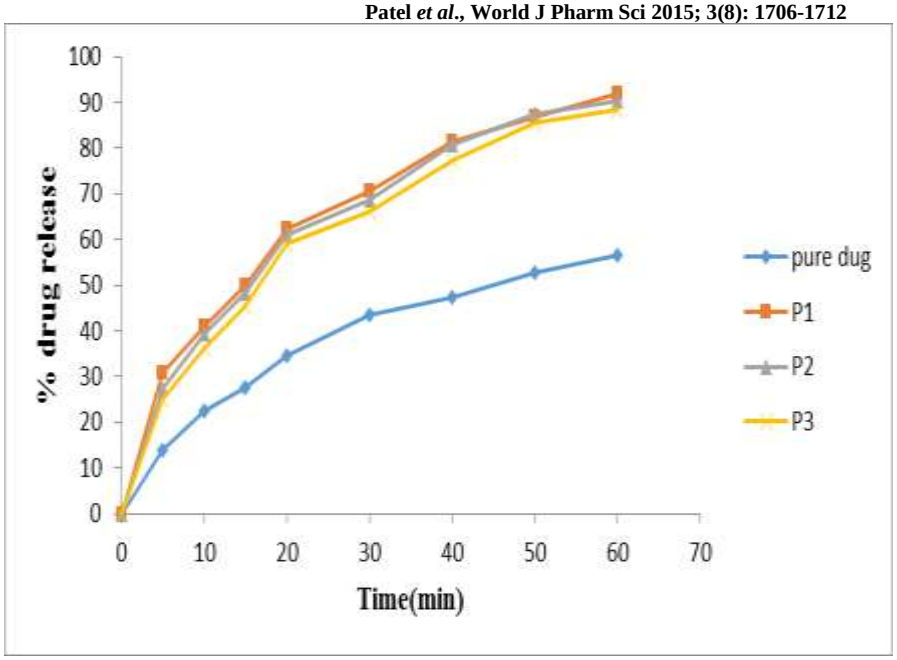

Figure 10. Percentage drug release of pure drug and physical mixture

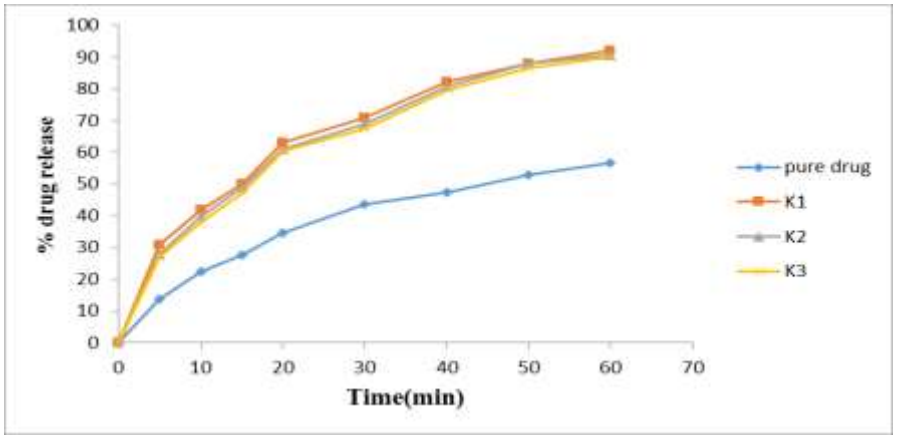

Figure 11. Percentage drug release of solid dispersion prepared by kneading method.

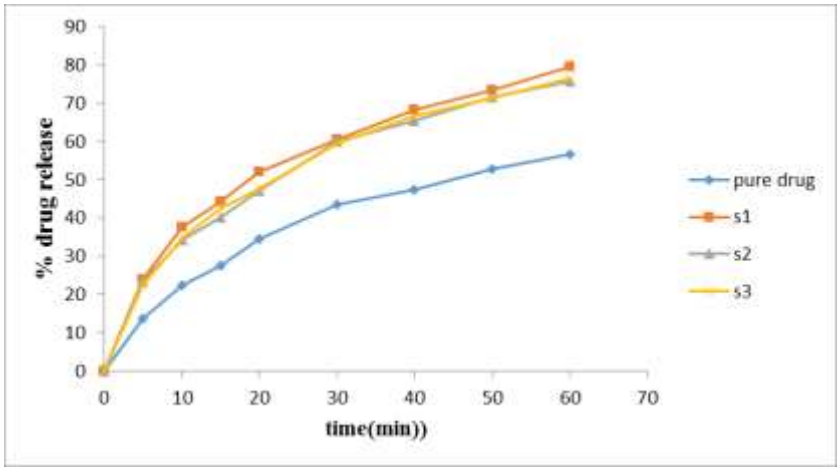

Figure 12. Percentage drug release of solid dispersion prepared by solvent evaporation method

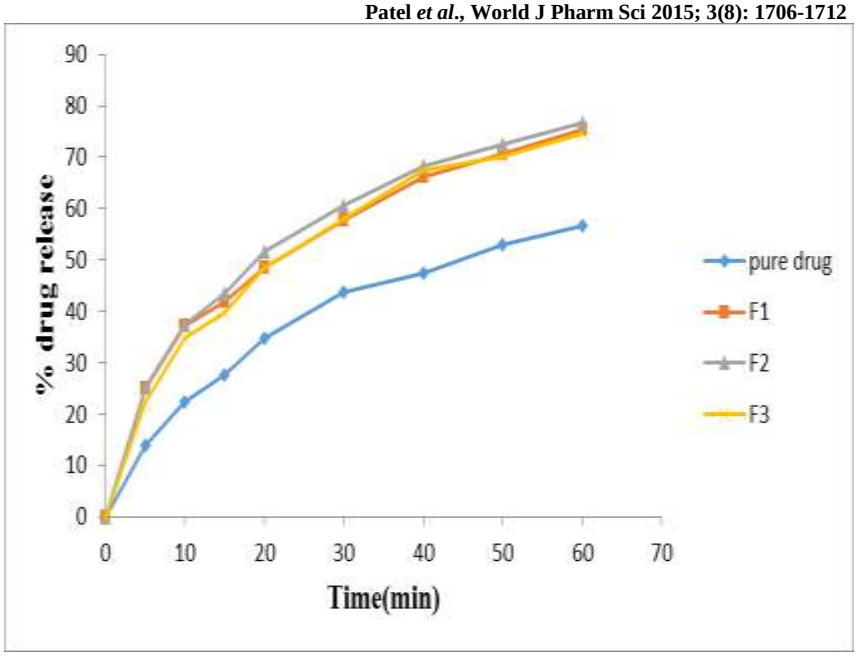

Figure 13. Percentage drug release of solid dispersion prepared by fusion method

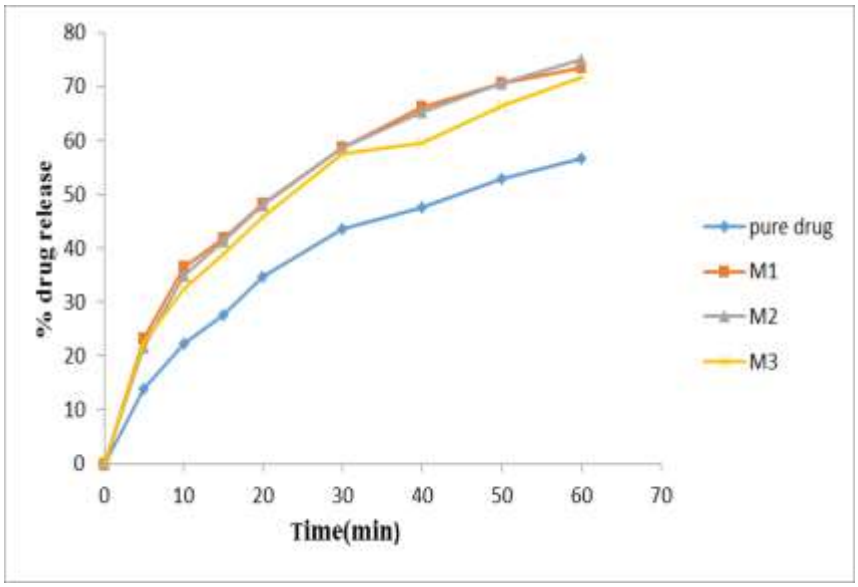

Figure 14. Percentage drug release of solid dispersion prepared by microwave induces sradiation.

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