

COMPARISON AND CHARACTERIZATION OF INCLUSION COMPLEXES AND SOLID DISPERSIONS IN ENHANCEMENT OF DISSOLUTION RATE OF POORLY WATER SOLUBLE DRUG

RADHA RANI EARLE^{1*}, RAMBABU JAMMU², A. LAKSHMI USHA¹, RATNA KANTH LINGAM¹

¹Department of Pharmaceutical Technology, Maharajah's College of Pharmacy, Vizianagaram, A. P., India, ²Leiutis Pharmaceutical Pvt Ltd, Hyderabad, Telangana
Email: radhaearle@yahoo.com

Received: 30 Jan 2018, Revised and Accepted: 26 Jul 2018

ABSTRACT

Objective: The purpose of the present study was to enhance solubility and dissolution characteristics of indomethacin by preparing inclusion complexes with hydroxypropyl β -cyclodextrin (HP β -CD) and solid dispersions with PEG 6000 to enhance its *in vitro* drug release and to further formulate it as a tablet

Methods: Solid dispersions (SDs) and inclusion complexes (ICs) of Indomethacin with PEG 6000 and HP β -CD respectively were prepared to enhance the dissolution rate of this poorly water-soluble drug belonging to BCS class II. A comparison was made between two systems: solid dispersions with PEG 6000 obtained using melting and solvent evaporation technique, inclusion complexes with HP β -CD prepared by kneading technique. SDs were prepared in 1:1, 1:2, 1:3 and ICs in 1:0.25, 1:0.5, 1:1 w/w ratios of drug: polymer. Both the systems were characterized by FTIR, SEM, DSC, X-RD.

Results: The dissolution of indomethacin increased with the increase in the concentration of the polymers. F4 and F9 formulations showed complete drug release in less than 30 min. Dissolution studies indicated that cyclodextrin complexes showed a better enhancement of dissolution rate when compared to solid dispersions. CDs were found to be more effective than PEGs at lower concentrations. These formulations were further compressed as tablets.

Conclusion: The FTIR and DSC studies showed that no interactions existed between the drug and the polymer.

Keywords: Cyclodextrins, Polyethylene glycols, Dissolution rate, Solubility enhancement, Anti-inflammatory

© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open-access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)
DOI: <http://dx.doi.org/10.22159/ijap.2018v10i5.25054>

INTRODUCTION

On the basis of two parameters: aqueous solubility and membrane permeability, the Biopharmaceutical Classification System (BCS) categorizes the drugs into four classes. Drugs belonging to BCS class II show low solubility and high permeability, thus requiring larger doses on oral administration to obtain therapeutic plasma concentration. At the site of absorption, as a drug requires being available in solution form, dissolution becomes a rate-limiting step. Hence, improving solubility and thus oral bioavailability of such drugs by formulation design approaches prove to be promising [1]. In the formulation development of new chemical entities, many approaches have been studied to enhance the dissolution rate of poorly soluble drugs by modifying the drug substance and creation of specific formulation [2].

Indomethacin represented in fig. 1 is a non-steroidal anti-inflammatory drug which also shows anti-pyretic action. It relieves pain related to inflammation or tissue injury. It inhibits prostaglandin synthesis and suppresses motility of neutrophils. The poor aqueous solubility of this drug limits its absorption and rate of dissolution which further decreases its bioavailability [3].

Polyethylene glycols (PEGs) have been widely employed in preparing solid dispersions because they melt at low temperatures, show less toxicity, compatibility with a wide range of drugs and hydrophilicity. Cyclodextrins are a group of structurally related oligosaccharides having an external surface which is hydrophilic and internal hydrophobic cavity. They are widely used to improve solubility and stability of drugs, the modified release kinetics of drugs, enhanced absorption and reduced side effects [4].

The present study was aimed at enhancing solubility and dissolution rate of poorly aqueous soluble drug indomethacin by preparation of solid dispersions and inclusion complexes in various w/w ratios of drug: polymer.

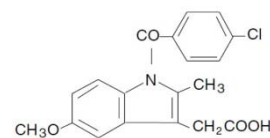


Fig. 1: Structure of Indomethacin

MATERIALS AND METHODS

Materials

Indomethacin, PEG 6000 were obtained from Yarrow Chem Products, HP β -CD, Sodium hydroxide were obtained from Finar Chemicals, ethanol and potassium di-hydrogen phosphate from Thermo Fisher Scientific India Pvt, Ltd (Mumbai, India).

Preparation of solid dispersions

Melting technique

In the preparation of solid dispersions of indomethacin by melting technique, drug and PEG 6000 were considered in w/w ratios of 1:1, 1:2 and 1:3. PEG 6000 was initially melted and the drug was added to the molten base. The molten mixture was thoroughly mixed and then rapidly cooled on an ice tray. On solidification, the mass was crushed and grounded with a mortar and pestle. The pulverized mass was passed through sieve no # 44. The product was stored in a desiccator until the next experiment [5].

Solvent evaporation

Different weight ratios of drug and carrier were dissolved in ethanol to obtain a clear solution. The solvent was removed by continuous stirring until a dry mass was formed. The obtained dry mass was further dried at 50 °C in an oven for about 4hours. The samples were powdered in a mortar, sieved through #60 mesh screen [6].

Preparation of inclusion complexes

Kneading technique

For the preparation of Inclusion complexes of indomethacin with HP β -CD by kneading technique, required quantities of drug and

polymer were triturated in a mortar by addition of little quantity of solvent consisting of a blend of water: ethanol (9:1). The thick slurry obtained was kneaded for a time period of 45 min and dried at 55 °C. The dried mass was powdered and sieved through #60 mesh [7]. All the formulations were mentioned in table 1.

Table 1: Formulation of solid dispersions and inclusion complexes

Formulation code	Polymers used	Drug: Polymer	Method of preparation
F1		Pure drug	
F2	PEG 6000	1:1	Melting technique
F3	PEG 6000	1:2	Melting technique
F4	PEG 6000	1:3	Melting technique
F5	PEG 6000	1:1	Solvent evaporation
F6	PEG 6000	1:2	Solvent evaporation
F7	PEG 6000	1:3	Solvent evaporation
F8	HP β -CD	1:0.25	Kneading technique
F9	HP β -CD	1:0.5	Kneading technique
F10	HP β -CD	1:1	Kneading technique

Drug content determination

Percent drug content was estimated by dissolving quantities equivalent to 50 mg of indomethacin in 100 ml of ethanol. The solutions were further diluted with 7.2 phosphate buffer and sonicated for about 15 min; drug content was analyzed at 265 nm by UV spectrophotometer. The actual drug content was calculated using the following equation [8].

$$\% \text{ Drug release} = \frac{\text{Actual amount of drug}}{\text{Theoretical amount of drug}} \times 100$$

In vitro dissolution

Dissolution studies of Indomethacin in powder form; from its solid dispersions and inclusion complexes was studied using Electro lab dissolution rate test apparatus with a paddle stirrer. The quantity of samples equivalent to 50 mg of drug was dispersed into the dissolution vessel containing 900 ml of phosphate buffer (pH 7.2). At

predetermined sampling intervals, 5 ml samples were withdrawn using a syringe fitted with 0.45 μ m filters. 5 ml of pre-warmed (37 °C) dissolution medium was added to the dissolution vessel in order to maintain a constant volume throughout the test. The samples were analyzed using UV visible spectrophotometer at 265 nm. Dissolution experiments were conducted in triplicate (n=3). Drug concentration was calculated and expressed as cumulative percent of the drug released [9].

Preparation of tablets

The optimized formulations F4 and F9 showing highest drug release were compressed into tablets as per the formula given in table by direct compression technique. All the dry ingredients were passed through sieve no # 44, transferred to a poly bag and blended to form a homogeneous mixture. To this, magnesium stearate pre-sifted through # 60 was added and blended. The final blend was compressed in a tablet punching machine [10]. The formula for preparation of tablet was mentioned in table 2.

Table 2: Formulation of tablets

Formulation code	Drug/SD/IC equivalent to 50 mg drug	Starch	Lactose	Starch	Magnesium stearate	Total
F1	50	50	190	5	5	300
F4	150	50	90	5	5	300
F9	75	50	165	5	5	300

Evaluation of tablets

The prepared tablets were evaluated for various parameters like hardness, weight variation friability and drug disintegration.

Characterization

Fourier-transform infrared spectroscopy (FTIR)

The FT-IR spectra were scanned over a frequency range of 4000-400 cm^{-1} . About 10 mg of samples were gently ground and mixed with IR grade dry potassium bromide. They were compressed at a pressure of 5 tons in a hydraulic press for 5 min to obtain discs and analyzed in FT-IR spectrophotometer. FTIR spectroscopy is used to detect any possible interaction between drug and polymer used [11].

Differential scanning calorimetry (DSC)

About 2 mg of Indomethacin or its equivalent was accurately weighed and placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10 °C min^{-1} from 50 to 300 °C [12].

X-Ray powder diffraction (XRD)

Samples were irradiated with monochromatized Cu K radiation (1.542 Å) and analyzed between 2° and 40° (2 θ). The voltage and current used were 40 kV and 30 mA, respectively. The chart speed was 10 mm/s [13].

Scanning electron microscopy (SEM)

The morphology of prepared products was investigated by scanning electron microscopy at an accelerating voltage of 1.0 kV [14].

Dissolution study

In vitro dissolution studies of the tablets were carried out in USP dissolution apparatus type II by employing a paddle stirrer at 100 rpm using 900 ml of pH 7.2 phosphate buffer at 37 \pm 0.5 °C as a dissolution medium. One tablet was used in each test. Aliquots of 5 ml each were withdrawn at specified time intervals (5, 10, 15, 30, 45, 60 min) and replaced with 5 ml volume of fresh medium. The withdrawn aliquots were analyzed for drug content spectrophotometrically at λ_{max} 265 nm. Comparison of dissolution profile was done to quantify the difference in rate and extent of drug release influenced by the addition of excipients and process variables [15, 16].

RESULTS AND DISCUSSION

Drug content determination

Drug content was found to be 98.54 \pm 0.63% and 99.89 \pm 0.84% respectively for formulations F4 and F9.

In vitro dissolution studies

All the formulations were subjected to *in vitro* dissolution using phosphate buffer (pH 7.2) as a dissolution medium. All the SDs and

the ICs exhibited higher dissolution rate when compared to pure indomethacin drug. The drug dissolution data was given in fig. 2 and 3. The pure drug showed the release of 51.79% in 60 min while formulations F4 and F9 showed complete drug release in 30 min. F4 was formulated in 1:3 w/w ratio of drug: polymer while F9 was formulated as 1:0.5 w/w ratio. HP β -CD was considered as a better polymer for enhancement of solubility of indomethacin, a poorly water-soluble drug as it was more effective at a lower concentration.

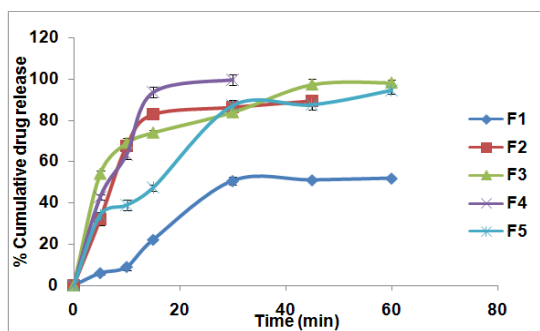


Fig. 2: *In vitro* drug dissolution for formulations F1-F5

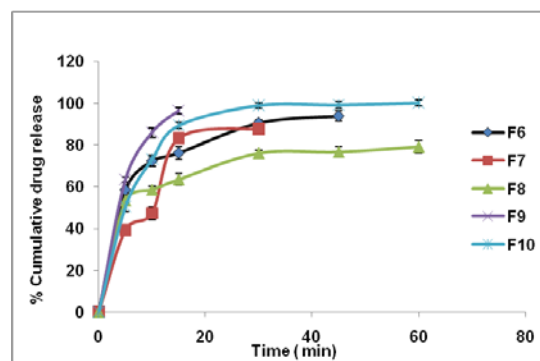


Fig. 3: *In vitro* drug dissolution for formulations F6-F10

Evaluation of tablets

The prepared tablets were evaluated, and all the values were within the specified ranges. The hardness of the tablets was in the range of 4-6 kg/cm². The tablets passed the test for weight variation, content uniformity, and friability. The data for all the evaluation parameters were mentioned in table 3.

Table 3: Evaluation of tablets

Formulation code	Hardness	Weight variation	Friability
F1	5.5±1.64	303.07±0.64	0.64±0.23
F4	5.0±2.23	302.29±1.42	0.31±0.84
F9	4.8±1.06	299.15±2.30	0.46±0.58

Fourier-transform infrared spectroscopy (FTIR)

Presence of any interaction between the drug and the polymers used often leads to significant changes in the IR spectra of the drug-polymer mixture. IR spectra of indomethacin showed characteristic peaks at 2927.8 cm⁻¹ (C-H stretching vibrations), 1709.9 cm⁻¹ (C=O stretching vibrations), 1220.7 cm⁻¹ (asymmetric aromatic O-C stretching), 1066.0 cm⁻¹ (symmetric aromatic O-H stretching). A

significant broad peak in the IR spectrum of HP β -CD at 3334.1 cm⁻¹ indicates the presence of O-H functional group in cyclodextrins. F4 and F9 also exhibited the characteristic peaks of indomethacin with no additional peaks observed in the spectra, indicating retention of the chemical identity of indomethacin as shown in fig. 4. The FTIR spectra data confirmed that there was no alteration in the performance characteristics indicating compatibility of the drug and the polymers.

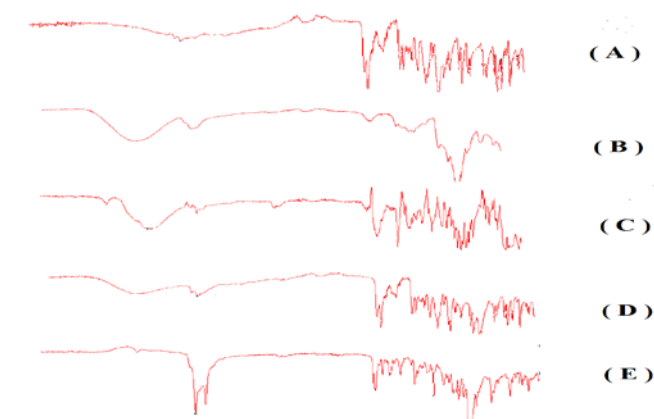


Fig. 4: FTIR overlay spectrogram of (A) Indomethacin, (B) HP β -CD, (C) PEG 6000, (D) drug inclusion complex with HP β -CD and (E) solid dispersion with PEG 6000

Differential scanning calorimetry (DSC)

The DSC thermogram of indomethacin exhibited a sharp endothermic peak at 162.16 °C corresponding to its melting point, indicating its crystalline nature. The onset of melting was obtained at 159.96 °C. The DSC curves of PEG 6000 and HP β -CD were obtained at 67.55 °C and 252.37 °C corresponding to their respective

melting points. These values meet with the values mentioned in the literature. In case of solid dispersion F4, the characteristic endothermic peak corresponding to the drug melting shifted towards lower temperature but retained the same peak intensity indicating the presence of the drug in crystalline form. DSC thermograms were overlaid and shown in fig. 5. It was observed that no interactions existed between the drug and the polymers used.

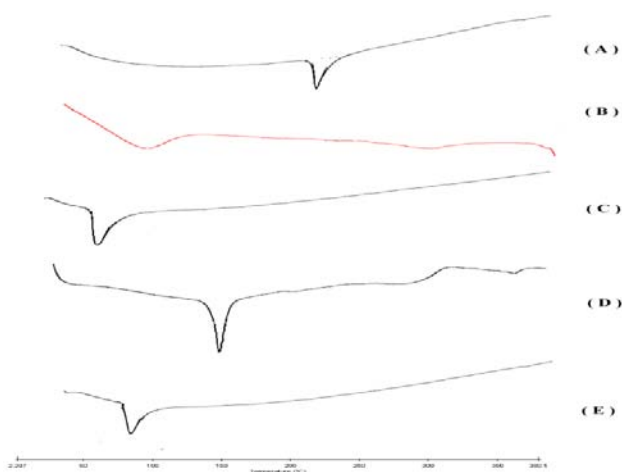


Fig. 5: DSC thermogram overlay of (A) Indomethacin, (B) HP β -CD, (C) PEG 6000, (D) drug inclusion complex with HP β -CD and (E) solid dispersion with PEG 6000

X-Ray powder diffraction (XRD)

The diffraction spectrum of pure indomethacin showed that the drug is highly crystalline powder and possesses sharp peaks. The absence of intense sharp peaks in F4 and F9 XRD indicated that the

crystalline form of the drug converted into amorphous form as shown in fig. 6. The decrease in the intensity of the diffractogram in case of formulations could be attributed to the destruction of crystal lattice structure of the drug, because of melting of drug into the carrier.

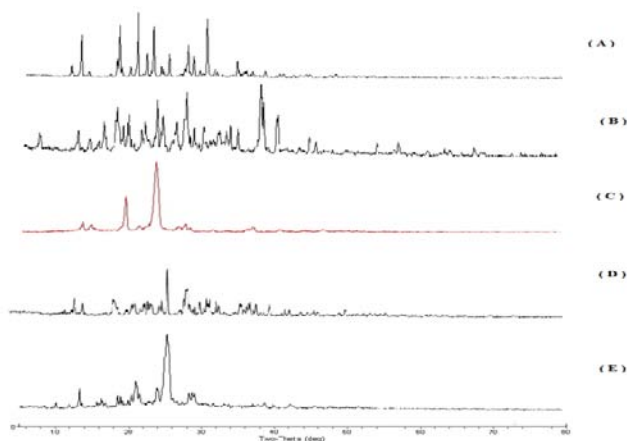


Fig. 6: XRD overlay of (A) Indomethacin, (B) HP β -CD, (C) PEG 6000, (D) drug inclusion complex with HP β -CD and (E) solid dispersion with PEG 6000

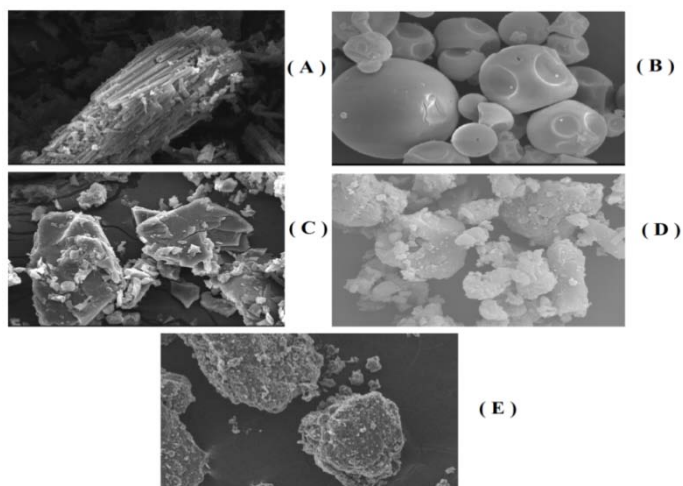


Fig. 7: SEM of (A) Indomethacin, (B) HP β -CD, (C) PEG 6000, (D) drug inclusion complex with HP β -CD and (E) solid dispersion with PEG 6000

Scanning electron microscopy (SEM)

SEM photographs are used to study the microscopic aspects of drug, polymers and the products obtained by melting, kneading etc. Indomethacin showed crystals which are regular in shape and size. SEM of HP β -CD showed regular and spherical structures while that of PEG 6000 showed the presence of crystalline structures. The inclusion complex and solid dispersion appeared like a matrix particle and are irregular in shape. This may be due to the dispersion of the drug in the polymer and conversion of a crystalline form of the drug into an amorphous form. All the SEM photographs were mentioned in fig. 7.

CONCLUSION

The solubility and dissolution rate of indomethacin can be enhanced by preparation of solid dispersions with PEG 6000 and inclusion complexes with HP β -CD. On the comparison between the two polymers, HP β -CD was found to enhance dissolution rate to an extent greater than in case of PEG 6000. FTIR and DSC studies revealed that there were no interactions between the drug and the polymers used. XRD studies indicated possible destruction in the crystal lattice structure of the drug. SEM studies showed that the regular crystalline structure of the drug converted into irregular forms indicating a complete dispersion of the drug in the carrier.

ACKNOWLEDGMENT

The authors would like to thank Dr. P. Udaya Shankar, Principal, Maharajah's College of Pharmacy, Vizianagaram for providing required facilities to carry out this research work. We are also thankful to Mr. Ranjit Prasad Swain, Assistant Professor, Maharajah's College of Pharmacy, Vizianagaram for his support and encouragement during this work.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors herewith declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

- Ahmed A, Sandra K, Karsten M. A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, *in vitro* digestion and incorporation into solid pellets. Eur J Pharm Sci 2008;35:457-64.
- Markus V, Klaus K, Jennifer BD. Dissolution improvement of four poorly water-soluble drugs by co-grinding with commonly used excipients. Eur J Pharm Biopharm 2008;68:330-7.
- Mahamoud ELB, Gihan F, Mohamoud F. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in gelucire 50/13 and PEG 4000. Saudi Pharm J 2009;7:217-25.
- Raymond CR, Paul JS, Marian EQ. Handbook of pharmaceutical excipients 6th edition; 2016. p. 210-214, 517-521.
- Punitha S, Vedha HBN, Karthikeyan D. Enhancement of celecoxib solubility by solid dispersion using mannitol. Int J Pharm Pharm Sci 2010;2:109-11.
- Ladan AN, Gurinder S, Gaurav S, Kimia FK. Solid dispersion: methods and polymers to increase the solubility of the poorly soluble drug. J Appl Pharm Sci 2012;2:170-5.
- Buchi NN, Chowdary KPR, Murthy KVR, Hayman AR, Becket G. Physicochemical characterization and dissolution properties of nimesulide-cyclodextrin binary systems. AAPS PharmSciTech 2003;4:1-12.
- Rajesh A, Pinkesh P, Sangeeta A, Chirag PJ, Jaiman P. Solubility enhancement of rifampicin by using liquisolid technique. Int J Pharm Res Bio-Sci 2013;2:203-18.
- Polli JE, Rekhi GS, Augsburg LL, Shah VP. Methods to compare dissolution profiles and a rationale for wide dissolution specification for Metoprolol tartrate tablets. J Pharm Sci 1997;8:690-700.
- Arun PK, Narayanan N, Rajalakshmi G. Preparation and evaluation of solid dispersion of terbinafine hydrochloride. Int J Pharm Sci Rev Res 2010;3:130-4.
- Rajesh K, Prasanna RY, Nagaraju R. Dissolution enhancement of valsartan using natural polymers by solid dispersion technique. Der Pharm Lett 2013;5:126-34.
- Sucheta B, Dyandevi M, Mithun VK, Rajendra DP. Solubility enhancement of the antihypertensive agent by solid dispersion technique. Int J Pharm Life Sci 2011;2:970-5.
- Sanjay JK, Anand U, Jasmine M, Vidula S. A modified solvent method for preparation of solid dispersion. Iranian J Pharm Sci 2011;8:287-98.
- Parve B, Balaji T, Avinash B. Studied on solid dispersions: an overview on Solubility enhancement of poorly water-soluble drugs. Int J Pharma Bio Sci 2014;5:7-25.
- Enhancement of dissolution rate and physicochemical characterization of irbesartan inclusion complexes using cyclodextrins. Res J Pharm Tech 2017;10:301-6.
- Tukaram K, Wadher SJ, Anitha K, Sominath D. Improvement of aqueous solubility and *In vitro* drug release rate of telmisartan using hydrophilic base by various dispersion techniques. Int J Pharm Tech Res 2016;9:28-34.