INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

SOLUBILITY ENHANCEMENT OF INDOMETHACIN BY SOLID DISPERSION TECHNIQUE AND DEVELOPMENT OF FAST DISSOLVING TABLETS

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Article Received on: 09/10/12 Revised on: 11/11/12 Approved for publication: 07/12/12

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ABSTRACT

Solid dispersion had become a potential candidate to overcome the poor solubility of drugs. The aim of the present study was to prepare and compare the dissolution profiles of pure indomethacin and its solid dispersions using PEG4000 and Gelucire 50/13 as carriers and development of FDTs. The solid dispersions were prepared by Melting method. The prepared SDs was subjected to solubility studies in pH 6.8 phosphate buffer. Drug content and dissolution studies of the prepared SDs and PMs were performed and quantification was done by UV/VIS spectrophotometric method at the absorption maximum 320 nm. The prepared SDs was characterized by FT-IR and DSC. Formulation F3 was selected for the Preperation of FDTs because of its maximum solubility, dissolution rates and appearance. Indomethacin FDTs were prepared by direct compression method, using various superdisintegrants croscarmellose, kyron and Indion. Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index and hausner ratio were carried out to study the flow properties of prepared blend to achieve uniformity of tablet weight and the values were within the limits., post-compression studies for the prepared tablets like hardness, weight variation, friability, drug content, wetting time, water absorption ratio, and *in vitro* disintegration time, *in vitro* dissolution profiles were performed., results obtained were satisfactory. Formulation T7 containing croscarmellose as superdisintegrant had shown the disintegration within 23 sec and highest release rate of 94.68% at the end of 15 min.

KEY WORDS: Indomethacin (IND), PEG 4000, Gelucire 50/13; Solid dispersion; Fast dissolving tablets; direct compression

INTRODUCTION

The solubility behaviour of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. In case of poorly water soluble drug, dissolution rate is rate limiting step in the process of drug absorption, potential bioavailability problem a relevant with extremely hydrophobic drug due to erratic and incomplete absorption from GIT. Potential absorption problem occur if the aqueous solubility is less than 1mg/ml. An estimated 40% of these drugs are poorly water soluble. Although most of the drugs have encouraging experimental data obtained *in vitro*, the *in vivo* results have been disappointing.

The attributes include

1. Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration,
2. Drug distribution to other tissues with high drug toxicities (anticancer drugs),
3. Poor solubility of drugs,

Fluctuations in plasma levels were owing to unpredictable bioavailability. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability[1]:

$$dC/dt = AD (Cs-C) / h$$

Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in bio relevant media. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. There are drug candidates that have poor solubility in water but can be dissolved by suitable conventional formulation strategies which include, Co-solvents, Milling techniques, super critical processing, Solid dispersions including Complexation, and precipitation techniques.

Solid dispersion technique has often proved to be the most commonly used in improving dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic and advantageous. In solid dispersion technique, water soluble carriers are used to improve dissolution characteristics of poorly water soluble drugs.

Several new technologies had been developed for oral delivery is being available to address to improve the patient compliance. Fast dissolving drug delivery system (FDDS) is gaining popularity in pharmaceutical companies as they are new drug delivery technique in order to provide the patient with medicine without obstacles in swallowing. FDDS include tablets and films. Fast dissolving tablets are designed in such a way that they disintegrate and then swallowed without the need of water as compared to other conventional dosage form[2].

USFDA defined FDTs as "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue"

Criteria for Formulating the Fast dissolving Tablets[3]

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Allow high drug loading.
- Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.

MATERIALS AND METHODS

Materials

Indomethacin was obtained as gift sample from Dr. Reddy's labs, Hyderabad. PEG4000 was obtained from SD fine chemicals, Mumbai. Gelucire 50/13 was obtained from Gattefosse SAS, saint priest, France. Kyron was obtained from Corel pharma, Mumbai. All other solvents and reagents used were of analytical grade.

Method

Solubility studies

The solubility study on IND was carried out in 6.8 pH phosphate buffers with carriers (PEG 4000, GEL 50/13) were performed by the method described by Higuchi and Connors. An excess amount of IND (approximately equivalent to 50 mg) was placed in screw capped container containing 50 ml of 6.8 pH phosphate buffer solutions of each polymer in various concentrations (1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:7). The suspensions were shaken for 24 hours on a water bath shaker at 37±1ºC and filtered through a 0.22µ membrane filter. The filtrates were diluted suitably with above mentioned solvent system and analyzed spectrophotometrically at 320 nm using Shimadzu UV- Visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

Preparation of Solid Dispersions[4]

Solid dispersions were prepared by Melting method. IND and PEG 4000, GEL 50/13 were weighed individually in various ratios (1:1, 1:2, 1:4, 1:7). IND was added to the molten base comprising PEG4000 or GEL 50/13. The blend was heated 10°C above the melting point of each carrier for 5 min with continuous stirring. The systems were placed in a freezer at 20°C for 24 h. The resulting solid dispersion was stored for 24 hrs in desiccators to congeal. Finally, dispersions were passed through sieve no.22 and stored in desiccators till further use.

Preparation of physical mixtures[5]

Gelucire is a waxy pellet, so it was crushed to fine particles firstly to prepare the physical mixture. Physical mixtures of IND with PEG 4000 or GEL 50/13 were weighed individually in various ratios (1:1, 1:2, 1:4, and 1:7). Weight ratio of IND: polymer, were prepared by blending them by triturating for 10 min followed by sieving.

Drug content

Solid dispersions equivalent to 50 mg of IND were weighed accurately and dissolved in a known quantity of 6.8 pH phosphate buffer. The solutions were filtered through a 0.22µ membrane filter. The filtrates were suitably diluted and drug content was determined spectrophotometrically at 320 nm using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

In-vitro dissolution studies

The quantity of solid dispersion equivalent to 50 mg of IND was weighed individually. The dissolution study of SDs were conducted using dissolution testing USP apparatus II (paddle method) in 900 ml of 6.8 pH phosphate buffer at 37±0.5ºC and at a speed of 75 rpm. Aliquot samples were withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain sink condition, after suitable dilutions analyzed spectrophotometrically at 320 nm against above mentioned buffers as blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

Characterization of solid dispersions

Differential Scanning Calorimetry (DSC)

Approximately 2-4 mg of pure IND, pure PEG 4000, GEL 50/13, and selected formulations were taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). The samples were scanned from 10-300°C with the scanning rate of 10°C/min using differential scanning calorimeter.

Fourier Transform Infrared Spectroscopy (FTIR)

The samples of pure IND, pure PEG 4000, GEL 50/13, physical mixtures of drug and polymers ratio, and selected formulations were prepared in the form of KBr pellets and subjected for scanning from 4000 to 400 cm^{-1} using FT-IR spectrophotometer.

Preparation of fast dissolving tablets of IND

Tablets containing 30 mg of IND were prepared by direct compression technique. The best SDs was selected and each ingredient was weighed individually and passed through sieve no 60. After passing each ingredient, all ingredients were mixed using a glass mortar and pestle. Powder blend were then directly compressed using 10 mm, round-shaped tooling in an eight station tablet compression machine (Riddhi Pharma instrument Ltd, Ahmedabad, India). This method was standardized for the preparation of different batches.

Wetting time

A piece of paper tissue (10.75 X 12 mm) folded twice was placed in a culture dish (d = 6.5 cm) containing 6 ml of 1% methylene blue solution. A tablet was kept on the paper, and the time for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined.

Disintegration test

The disintegration test was carried out using USP disintegration test apparatus type II. Six tablets were placed individually in each tube, and basket rack is positioned in a 900 ml beaker of distilled water was used as the medium. Which is maintained at 37$\pm$0.5°C and the time taken for each tablet to disintegrate completely was recorded.

In-vitro dissolution study

Dissolution study was carried out using USP dissolution test apparatus type II (Electro lab TDT-08L). The dissolution medium used was 900 ml of phosphate buffer of pH 6.8 and the temperature was maintained at 37±0.5º c. The paddle speed 50 rpm was maintained. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a sink condition. Filtered, diluted and assayed at 320 nm by measuring the absorbance against blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

Table 1: Solubility studies of solid dispersions

S.no	Formulations (Drug: Polymer)	With PEG4000 (mg/ml)	With Gelucire 50/13 (mg/ml)
1.	Indomethacin drug	0.0842	0.0842
2.	1:1	0.160	0.252
3.	1:2	0.248	0.344
4.	1:3	0.648	0.598
5.	1:4	1.006	0.838
6.	1:5	0.712	0.674
7.	1:7	0.370	0.718

Table 2: Drug content and dissolution rate of prepared formulations

S.no.	Formulations	Contents	Drug content (%)	Dissolution in 15 min
1.	F1	IND: PEG 4000	98.21±1.85	51.78%
2.	F2	IND: PEG 4000	100.61±1.05	45.81%
3.	F3	IND: PEG 4000	100.23±0.20	84.60%
4.	F4	IND: PEG 4000	97.21±1.01	50.92%
5.	F5	IND: GEL 50/13	97.25±1.54	69.01%
6.	F6	IND: GEL 50/13	97.88±1.68	66.80%
7.	F7	IND: GEL 50/13	98.22±1.46	69.04%
8.	F8	IND: GEL 50/13	100.11±1.90	66.79%
9.	F9	IND: PEG 4000	95.61±1.51	41.41%
10.	F10	IND: PEG 4000	96.24±1.23	59.08%
11.	F11	IND: PEG 4000	96.42±1.10	64.91%
12.	F12	IND: PEG 4000	96.02.±1.24	42.79%
13.	F13	IND: GEL 50/13	98.24±0.99	42.37%
14.	F14	IND: GEL 50/13	89.62±1.01	49.96%
15.	F15	IND: GEL 50/13	91.82±1.56	56.82%
16.	F16	IND: GEL 50/13	91.01±0.98	56.99%

Table 3: Selection parameters for formulating FDT

Formulation(IND: PEG 4000)	Drug content %	Dissolution	Solubility (mg/ml)
F3 (1:4)	100.23	84.60	1.006

Table 4: DSC interpretation of pure drug and solid dispersion

Samples (Coded)	Melting point (^{o}C) of Pure drugs and polymers Onset/peak/end set	Melting point (^{o}C) of formulations Onset/peak/end set
INDOMETHACIN (IND)	158.83/159.99/163.31	-
F3 (peg 1:4)	-	91.42/104.70/107.48

Table 5: Formulation table of Indomethacin FDT

Ingredients (mg/tablet)	T1	T2	T3	T4	T5	T6	T7	T8	T9
Indomethacin Solid dispersion	150	150	150	150	150	150	150	150	150
Mannitol	110	110	110	100	100	100	99	99	99
Croscarmellose	10	-	-	14	-	-	15	-	-
Kyron	-	10	-	-	14	-	-	15	-
Indion	-	-	10	-	-	14	-	-	15
MCC	24	24	24	30	30	30	30	30	30
Sucralose	2	2	2	2	2	2	2	2	2
Magnesium sterate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight (mg)	300	300	300	300	300	300	300	300	300

Table 6: Post-compression parameters of fast dissolving tablets of IND

Formulations	T1	T2	T3	T4	T5	T6	T7	T8	T9
Weight variation (mg)	298.85±2.39	299.85±2.64	298.10±2.93	298.85±2.39	299.85±2.64	298.10±2.93	300.70±2.15	299.30±1.59	300.15±1.46
Hardness (Kg/cm^2)	3.63±0.156	3.47±0.332	3.57±0.070	3.63±0.156	3.47±0.332	3.57±0.070	3.60±0.280	3.97±0.109	3.98±0.102
Friability (%)	0.75	0.68	0.61	0.75	0.68	0.61	0.51	0.63	0.60
Wetting time (sec)	41.66±2.08	42.33±3.21	46.66±2.51	41.66±2.08	42.33±3.21	46.66±2.51	35.33±2.08	36.66±2.51	34.66±2.08
Water abs ratio (%)	79.66±0.21	77.33±0.25	76.34±0.31	79.66±0.21	77.33±0.25	76.34±0.31	85.67±0.28	88.34±0.19	93.67±0.13
Drug content (%)	95.6±0.72	96.1±2.23	94.8±0.45	95.6±0.72	96.1±2.23	94.8±0.45	98.3±0.85	99.2±0.36	98.8±0.40

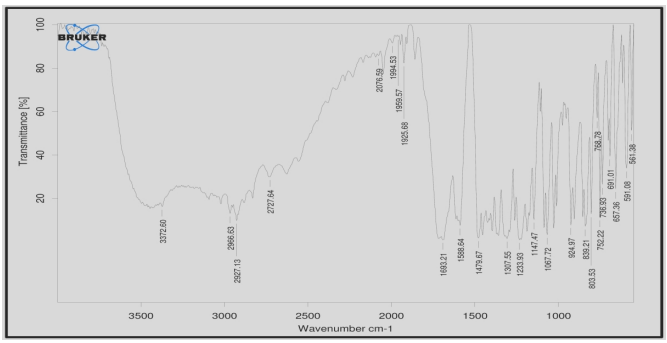

Figure 1: FTIR spectrum of pure indomethacin

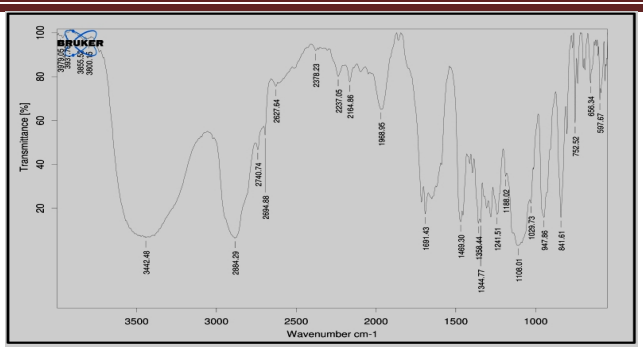

Figure 2: FTIR spectrum of solid dispersion F3 (Indomethacin: PEG 4000)

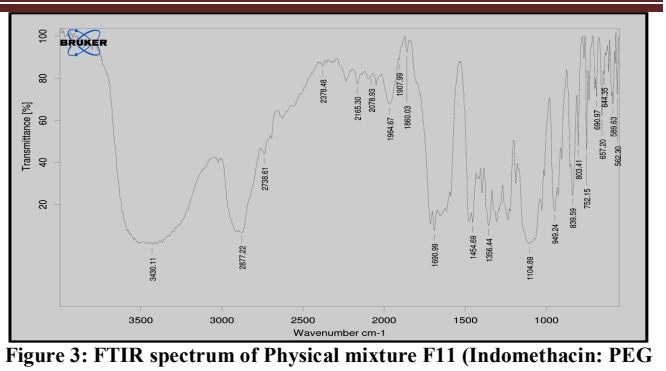

Figure 3: FTIR spectrum of Physical mixture F11 (Indomethacin: PEG 4000)

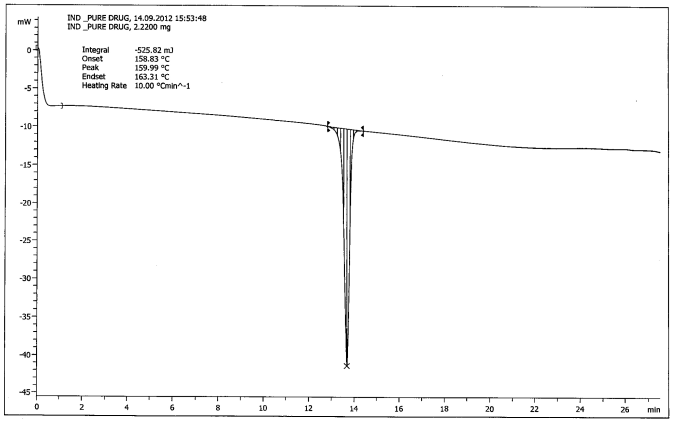

Figure 4: DSC Thermogram of pure Indomethacin

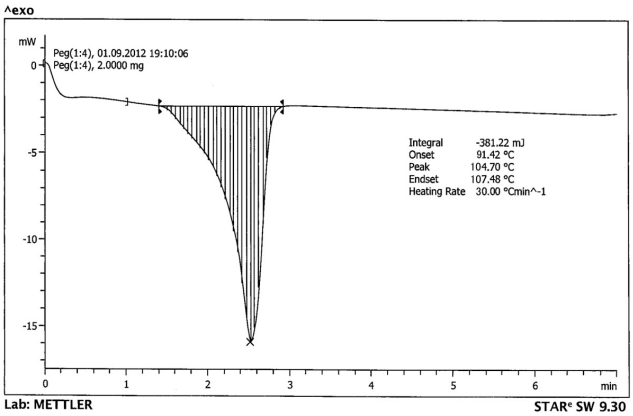

Figure 5: DSC Thermogram of solid dispersion F3 Indomethacin: PEG 4000(1:4)

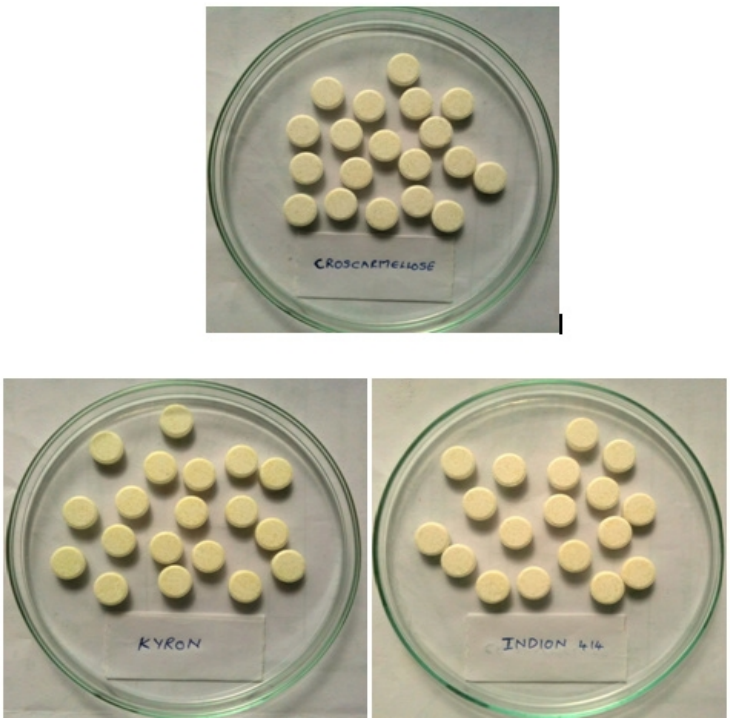

Figure 6: Prepared Indomethacin Fast dissolving tablets T7, T8, T9

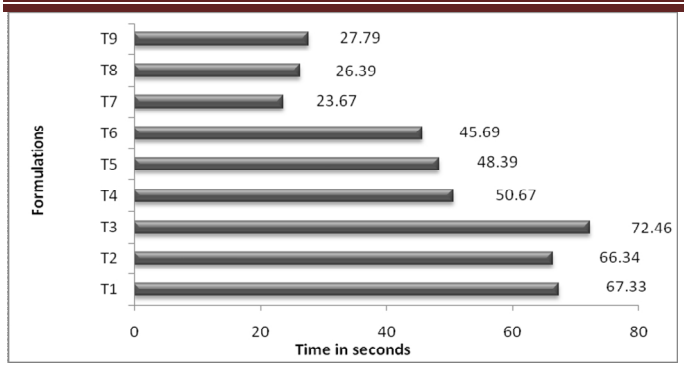

Figure 7: *In vitro* disintegration test of IND fast dissolving tablets

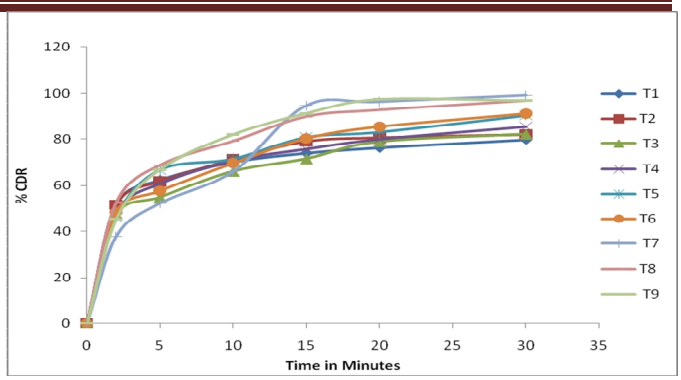

Figure 8: *In vitro* dissolution test of IND fast dissolving tablets

RESULTS & DISCUSSION

The objective of the present study is to enhance the aqueous solubility and dissolution rate of indomethacin by solid dispersion and to formulate the fast dissolving tablets.

Solubility Studies: The solubility enhancement of IND obtained with various carriers followed by PEG 4000> GEL 50/13. The solubility of GEL 50/13 was less than the PEG 4000 because; the solubility of drug may be dependent on the molecular weight of carrier. Solubility of IND increases as carrier concentration increases. The increase in solubility may be due to the wettability action of carriers.

Drug content of solid dispersions and physical mixtures: Solid dispersion of IND with PEG 4000, GEL 50/13 alone & combination of these carriers were prepared by physical mixture, melting method. The percentage of drug content of all the formulations varied from 89.62±1.01 to 100.23±0.20 % as shown in the Table 2. These results indicate that there was uniform distribution of the drug throughout the batch.

***In-vitro* dissolution studies of IND and its solid dispersions:** Dissolution studies of IND solid dispersions were carried out in 6.8 pH phosphate buffer to compare the percentage release rate of drug from solid dispersions. *In vitro* dissolution test results indicate complete dissolution of drug from all the solid dispersion within 20 to 30 min which is depicted in Table 2. Among the formulations, F3 had shown the release rate of IND in 6.8 pH buffer with 99.42±0.43%. The formulation F3 showed more dissolution rate as compared to other formulations. The enhanced dissolution rate may be due to enhanced wettability and dispersibility of drug in dissolution medium.

Characterization of Solid dispersions

FTIR studies: Spectrum of indomethacin along with selected formulations was taken and the characteristic peaks were shown in Figure 1, 2 and 3. the characteristic peaks were compared with the IR spectrum of the selected samples. The results of the FTIR analysis revealed that no interaction between drug and carriers.

DSC studies: The change in the melting point had suggestive that the formulated product is a mixture of the two molecules. Supporting the idea that formulation is a mixture of drug and polymer.

Pre compression parameters: The values for angle of repose were found in the range of 28°- 32°, Bulk densities and tapped densities of various formulations were found to be in the range of 0.551±0.005 (gm/ml) to 0.591±0.003 (gm/ml) and 0.587±0.015 (gm/ml) to 0.631±0.014 (gm/ml) respectively. Carr's index of prepared blend fall in the range of 5.50 % to 10.55 % Hausner's ratio of the prepared blend fall in the range of 1.05 to 1.11. From the results it was concluded that the powder blends had good flow properties.

Evaluation of Tablets

Wetting time: Wetting is closely related to inner structure of tablets and the hydrophilicity of excipients. The wetting time in all the formulation was very fast and acceptable. This may be due to ability of swelling and also capacity of absorption of water. Croscarmellose, Kyron and Indion absorb water rapidly in the formulation and showed fast wetting time. The result showed that the wetting time of the formulation was in the range of 23±3.5 to 46±2.51 sec.

Drug content uniformity: Drug content uniformity study was carried out on the tablets of every batch.. The content uniformity of all the formulations was found to be in the range of 94.80±0.45 to 100.1±0.86%, which showed that there was uniform distribution of the drug through the batch.

***In vitro* disintegration time:** Tablets of each batch were evaluated for *in vitro* disintegration time and the data's were shown in Fig 7. The results showed that the disintegration time of prepared tablets were in the range of 23.67±2.08 to 66.34±4.50 sec. The tablets of batch T7 prepared by using 5% of croscarmellose showed 23±2.08 sec, the tablets of batch T8 prepared by using 5% of kyron showed 26.3±3.78 and the tablets of batch T9 prepared by using 5% Indion had the disintegration of 27.7±1.52. Among all the prepared formulations, T7 containing croscarmellose as superdisintegrant have the better disintegration.

***In vitro* dissolution studies:** The *in-vitro* dissolution studies were conducted in phosphate buffer pH 6.8 and their release were shown in Fig 8. The Formulation T7 contains croscarmellose superdisintegrant showed maximum 94.68% of drug release within 15 min, while the formulations T8 and T9 with kyron and indion had showed 90.06% and 91.28% of release; the formulation T7 had release 99.15% respectively at 30 minutes. This result exhibits superdisintegrants with low concentration is highly effective. The formulations T7, T8 and T9 had released the drug most affectively with in the 15 minutes interval at a maximum rate of >90% release.

CONCLUSION

Solid dispersions prepared by melting method were satisfactory. The solubility studies of indomethacin solid dispersions in presence of PEG 4000 and Gelucire 50/13 had showed increased solubility, Concentration with 4% had showed the highest solubility. From drug content and *in vitro* dissolution studies of indomethacin solid dispersions, It was concluded that the formulation F3 i.e., the solid dispersion of Indomethacin with PEG 4000 (1:4) prepared by melting method was found to be best formulation. From the Differential scanning Calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), it was concluded that there is no interactions in the solid dispersion formulations was

observed. The FDT formulations of Indomethacin were prepared by direct compression method by using different superdisintegrants (croscarmellose, Kyron, Indion) were prepared. Overall FDT containing superdisintegrant croscarmellose appears to be the best formulation. The rank order for the superdisintegrants is as follows croscarmellose > Kyron > Indion. The post compression parameters of all formulations were determined and the values were found to be within pharmacopoeia limits. Direct compression method is the best-suited method for formulation of FDT of Indomethacin. Upon increasing the concentrations upto 5% the disintegration was effective. This would be an effective and advanced approach to solublize the poorly soluble drug indomethacin by solid dispersion technique and to deliver the drug instantly within a matter of seconds, by developing fast dissolving tablets with use of less expensive adjuvants and sophisticated instruments in the formulations. Thus it may be concluded that the SD's and development of FDT's of Indomethacin can be successfully prepared and evaluated.

ACKNOWLEDGEMENT

The authors thank Dr. Reddy's Laboratories, Hyderabad, for providing Indomethacin as gift sample for this work. They also thank Head of the institutions and CM Ravi kiran, secretary, East west group of Institutions, Bangalore for providing required facilities to carry out this research work.

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Source of support: Nil, Conflict of interest: None Declared