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Formulation and Characterization of Sustained Release Matrix Tablets of Indomethacin Using *Moringa Oleifera* Gum

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Abstract: Solid dispersion techniques have been used during the past few decades to increase solubility and bioavailability of poorly soluble drugs. In recent years in addition to solubility and bioavailability enhancement more attention has been paid to use solid dispersion techniques for the development of sustained release dosage forms. The solid dispersion techniques have a great potential in the area of sustained release dosage form design because of availability of wide variety of carriers. Hydrophilic natural polymers are widely used in the formulation of oral dosage forms. Their ability to hydrate and form a gel layer are well known and essential to retard the drug release from the formulation. Hence the work was planned for selection, extraction and purification of natural gum Moringa oleifera. Indomethacin solid dispersions were prepared by using PEG 8000 as a carrier by employing solvent evaporation method and melting method. Further matrix tablets were prepared with 5%, 10%, 15% of natural polymer like Moringa oleifera, synthetic and semi synthetic polymers like HPMC K15 and Eudragit RL100. Tablets prepared were evaluated for the release of indomethacin over a period of 12 h in pH 7.2 phosphate buffer using US Pharmacopoeia type II dissolution apparatus. The in vitro drug release study revealed that the tablet containing Moringa oleifera gum has extended the release rate for 12 h whereas the tablet containing HPMC K15 and Eudragit RL100 at the same concentrations was not extended the release rate up to 12 h.

Keywords - Indomethacin, *Moringa oleifera*, PEG 8000, Solid dispersions, Sustained release matrix tablets.

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I. INTRODUCTION

Indomethacin, an indole derivative is a widely used NSAID (Non-steroidal anti-inflammatory drug). It is a BCS class II drug (poor water soluble and high biomembrane permeable) and has a short half life of about 2-5 h make it an ideal candidate for sustained release. A once daily sustained release formulation of indomethacin is useful to reduce the frequency of administration, to minimize the gastrointestinal disturbances and to improve patience compliance[1, 2, 3, 4, 5].

So many studies have been reported in the literature for the preparation of delayed release formulations using solid dispersion techniques[6, 7, 8]. The solid dispersion techniques can be used to improve the dissolution rate of poorly water soluble drugs as well as to sustain the drug release by selecting suitable polymers[9, 10, 11, 12, 13].The sustained release solid dispersions are generally prepared by any of the methods where the ingredients are dissolved in a solvent followed by drying or by melting the active and inert ingredients together followed by solidification or combination of the two methods. Preparation of matrices with water insoluble and water swellable polymers using solid dispersion technique is a valuable method in the production of delayed release products [14, 15, 16]. Recent works demand the replacement of synthetic excipients with natural and nontoxic products.

In the present study, the exudates from the stem of the tree *Moringa oleifera* was investigated for its application as a release retardant in tablet formulation[17]. As indomethacin is a poorly soluble drug it is made soluble by preparing solid dispersions with PEG 8000 as carrier by employing melting method and solvent evaporation method. Indomethacin sustained release tablets were prepared by using natural gum *Moringa oleifera*, synthetic polymer HPMC and semisynthetic polymer Eudragit RL 100 by employing direct compression method.

II. MATERIALS AND METHODS

2.1. Materials

Indomethacin was purchased from Yarrow Chemicals, Mumbai. *Moringa oleifera* gum was collected from local areas in Vizianagaram. PEG 8000, HPMC K15, Eudragit RL 100 was received from Yarrow Chemicals, Mumbai, and all the other chemicals used were of analytical grade.

2.2. Methods

2.2.1. Extraction and Purification of *Moringa oleifera* Gum

The gum was collected from the stem of *Moringa oleifera* trees (injured site) in the local areas of Vizianagaram. It was dried, grounded and passed through sieve number 85. Dried gum (10 g) was stirred in hot water (200 ml) for 30 m in a mechanical stirrer. The supernatant was obtained by centrifugation. The residue was treated with twice the volume of ethanol by continuous stirring. The precipitated material was collected by filtration. The collected filterate was dried at 50°C, covered and stored in a desicator.

2.3. Characterization Studies

2.3.1. Fourier Transform Infrared Spectroscopy (FTIR)

Drug- polymer interactions were studied by FTIR spectroscopy using the instrument IR-Prestige-21, Shimatzu, Japan. The spectra were recorded for samples. Samples were placed in KBr discs (2 mg sample in 200 mg KBr) with a hydrostatic press at a force of 5.2 N/m^2 for 3 m. The scanning range was 400-4000 cm^{-1}.

2.3.2. Differential Scanning Calorimetry (DSC)

DSC was used to investigate and predict any physicochemical interactions between components in a formulation and therefore can be applied to the selection of suitable chemically compatible excipients. The DSC measurements were performed by using differential scanning calorimeter Pyris Diamond TG/DTA, Perkin Elmer, Singapore. Samples of about 5 mg were placed in 50 µl perforated aluminium pans and sealed. All samples were run at a heating rate of 10 °C/m over a temperature range of 5-300°C in atmosphere of nitrogen as purging gas at a flow rate of 25 ml/m.

2.3.3. X-ray Diffraction (XRD)

The drug carrier interactions and physical state of the drug were determined with the help of XRD. XRD patterns were obtained by using an X-ray diffractometer- PW 170 system (Philips USA) with Cu-Kα radiation (400 kV, 30 mA and scan speed 1 °C/m) to investigate the physical state of sample.

2.4. Preparation of Solid Dispersions

According to the formulae (Table No.1) solid dispersions were prepared by solvent evaporation method and melting method at the drug with polymer ratios of 1:0.5, 1:1, 1:2, 1:3. Dissolution studies were conducted and better ratios were used for compression of sustained release matrix tablets.

Table No.1. Formulae for Preparation of Solid Dispersions

Formulation Code	Carriers	Method	Drug:Polymer ratio
S1	PEG 8000	Solvent evaporation	1:0.5
S2	PEG 8000	Solvent evaporation	1:1
S3	PEG 8000	Solvent evaporation	1:2
S4	PEG 8000	Solvent evaporation	1:3
S5	PEG 8000	Melting	1:0.5
S6	PEG 8000	Melting	1:1
S7	PEG 8000	Melting	1:2
S8	PEG 8000	Melting	1:3

2.4.1. Solvent Evaporation Method

The ingredients were weighed accurately. Dissolve the drug in ethanol and polymer in water separately. Mix the two solutions and adjust the heating plate temperature up to 60°C, then the solutions were placed on the heating plate, stirr continuously until the product become a solid mass. Immediately placed it an ice-bath followed by continuous stirring. Finally placed in a desiccator upto 24 h, scrap it and pass through the sieve number 44, sealed in a self sealable cover for further use.

2.4.2. Melting Method

The thermostatic water bath was filled with water upto required level and bath temperature was adjusted according to the melting point of the polymer (PEG 8000, melting point 60°C). Accurately weighed

quantity of polymer was melted and then the drug was added with continuous stirring. The formulation was placed into the ice-bath for solidification and kept in desiccator up to 24 h, it was then scrapped and passed through sieve number 44, sealed in a self-sealable cover for further use[18].

2.5. Preparation of Tablets

Table No.2. Composition of Indomethacin Solid Dispersion Sustained Release Matrix Tablets

Ingredients	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid dispersions (S3) equivalent to 75 mg of indomethacin	225	225	225	225	225	225	225	225	225	225
Moringa oleifera gum	-	15	30	45	-	-	-	-	-	-
HPMC K15	-	-	-	-	15	30	45	-	-	-
Eudragit RL100	-	-	-	-	-	-	-	15	30	45
Microcrystalline cellulose	66	51	36	21	51	36	21	51	36	21
Magnesium stearate (2%)	6	6	6	6	6	6	6	6	6	6
Talc (1%)	3	3	3	3	3	3	3	3	3	3

Total tablet weight = 300 mg

Note**:** Formulations F0 was formulated without polymers, F1-F3 were formulated with 5%, 10%, 15% of *Moringa oleifera* gum and F4-F6 were formulated with 5%, 10%, 15% of HPMC K15 and F7-F9 were formulated by using 5%, 10%, 15% of Eudragit RL 100.

2.6. Pre compression studies

Precompression parameters like angle of repose, bulk density, tapped density, Carr's index and Hauser's ratio were determined before compression of tablets.

2.7. Compression of tablets

Matrix tablets of indomethacin were prepared using direct compression method. The formulae of various formulations from F0-F9 (Table No.2) were passed through sieve number 44, weighed accordingly and mixed geometrically (except glidant and lubricant). Indomethacin solid dispersions were mixed with its respective polymer, then directly compressible vehicle was added and mixed properly. Finally glidant and lubricant were added just before compression. The mixture was then compressed using a 12 station rotary tablet machine equipped with round, flat punches of 10 mm diameter. The tablets thus formed were protected from moisture and light.

2.8. Post compression studies

The prepared tablets were evaluated for weight variation, hardness, friability and drug content. Hardness of tablets was determined by using a Monsanto tablet hardness tester (Shiv scientific stores). Friability test was conducted using Roche friabilator (Roche friabilator, DBK instruments). The drug content of the manufactured tablets were estimated by using UV spectrophotometric method. From each batch, 20 tablets were taken, weighed and finely powdered. A required quantity of this powder equivalent to 10 mg of the drug was accurately weighed, dissolved, diluted and analysed by UV spectrophotometric method at 320 nm (Cary 60, Agilent, USA).

2.9. *In vitro* Drug Release Studies

The dissolution study was carried out by operating dissolution apparatus (Disso 2000 LAB INDIA, Mumbai). The USP dissolution apparatus with rotating paddle assembly (apparatus II) was used at 100 rpm, with 900 ml of phosphate buffer of pH 7.2 and maintained a temperature at 37±0.5°C throughout the study. The mean of the three determinations were used to calculate the drug release from the formulation. The samples were withdrawn at a predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h) and equal amount (5 ml) of fresh buffer was replaced. The obtained sample was filtered and assayed spectrophotometrically at 320 nm.

2.10. Release kinetics

Analysis of variance, model independent and model dependent approaches were used for comparison of dissolution profiles.

In model dependent approaches release data was fitted to five kinetic models including zero order, first order, Higuchi model, Peppas-Korsmeyer and Hixson-Crowell release equations to find out the equation with the best fit [19, 20, 21, 22].

$$Qt = Qo + Kot \quad (1)$$

$$logC = logCo - \frac{Kt}{2.303} \quad (2)$$

$$ft = Q = K_H \times t^{1/2} \quad (3)$$

$$\frac{M_t}{M_\infty} = Kt^n \quad (4)$$

$$W_0^{1/3} - W_t^{\frac{1}{3}} = kt \quad (5)$$

III. RESULTS AND DISCUSSION

2.11. Preformulation Parameters of *Moringa oleifera* Gum

Moringa oleifera gum was extracted and purified according to the procedure. This was previously evidenced by Panda *et al* [23]. All the preformulation studies were performed in triplicate as per specifications (Table No.3). These were previously evidenced by Dibya *et al* [24].

Table No.3.Preformulation Parameters

Parameter	Observation
Colour	Brownish black
Odour	Characteristic
pH (1% w/v)	6.85
Moisture content	4%
Swelling index	1 ml/g
Solubility	Sparingly soluble in water, insoluble in organic solvents
Angle of repose	30.794°
Bulk density	0.54 g/cm^3
Tapped density	0.75 g/cm^3
Carr's index	28%
Hausner's ratio	1.388
Yield (100 g)	12 g

2.12. Characterization studies

2.12.1. Fourier Transform Infrared Spectroscopy

The FTIR spectrum of all the combinations containing physical mixture was resulted in similar or slightly shifted in peak values, when compared with the characteristic peaks value of pure drug. The results shown below in the Fig.1a, 1b, 1c, 1d, reveal that there was no major interaction between drug and physical mixture and hence the excipients can be safely used to formulate sustained release tablets containing solid dispersions.

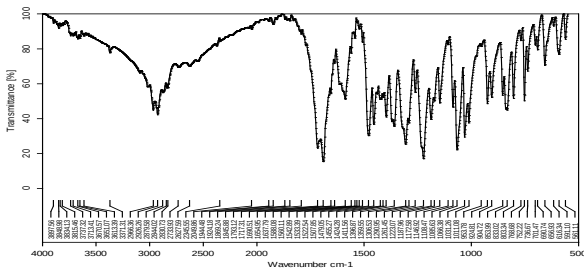

Figure.1a.IR spectrum for indomethacin

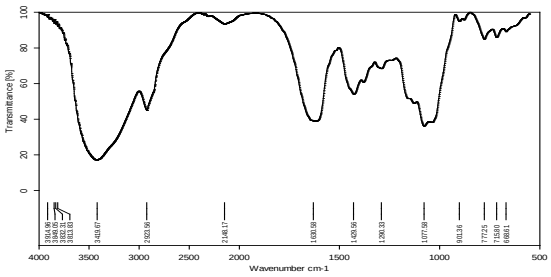

Figure.1b. IR spectrum for *Moringa oleifera* gum

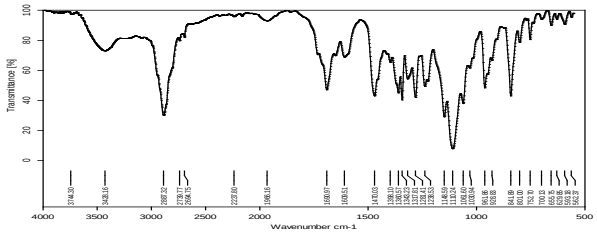

Figure. 1c.IR spectrum for solid dispersions

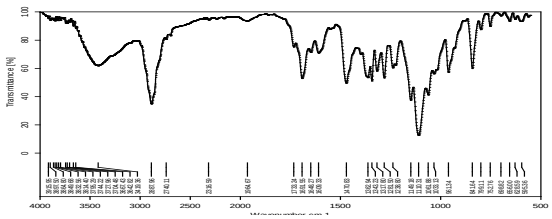

Figure.1d. IR spectrum for physical mixture

2.12.2. Differential Scanning Calorimetry

The peak of indomethacin was shifted to lower values indicating that most of the drug in amorphous form as represented in the Fig. 2a, 2b, 2c, 2d . This could be attributed to higher carrier concentration and uniform distribution of drug in the carrier resulting in complete miscibility of carrier.

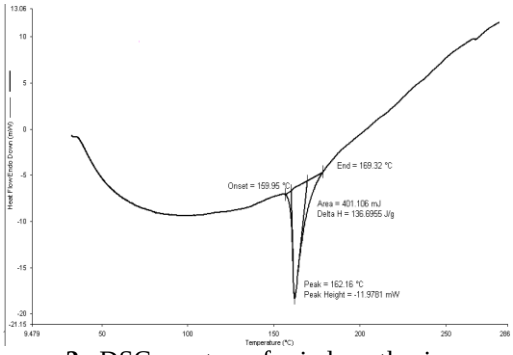

Figure. 2a.DSC spectrum for indomethacin

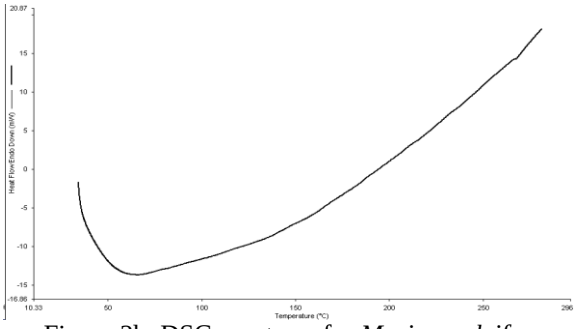

Figure.2b. DSC spectrum for *Moringa oleifera* gum

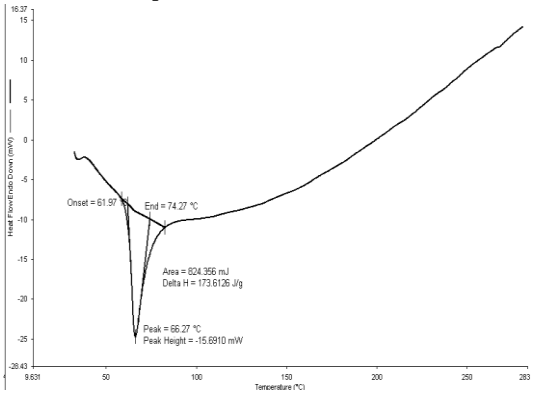

Figure. 2c.DSC spectrum for solid dispersion

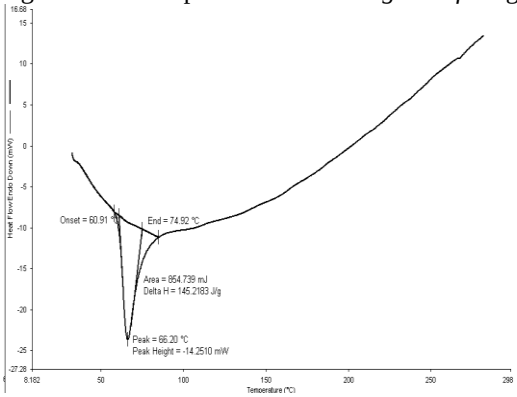

Figure. 2d. DSC spectrum for physical mixture

2.12.3. X-ray Diffraction

The pure drug showed intense peaks at two theta and corresponding degree it showed crystallinity of indomethacin, in the Fig. 3a. Absence of intense of sharp peaks in solid dispersion XRD indicated that crystalline nature of drug converts into amorphous form in Fig. 3b.

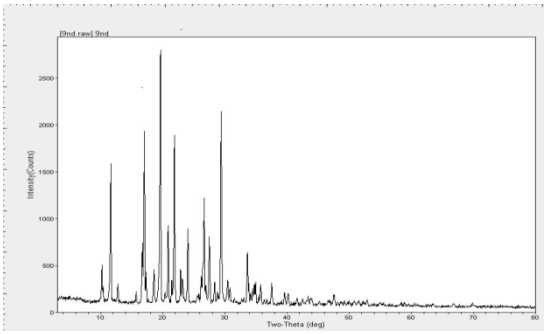

Figure.3a.XRD spectrum for physical mixture

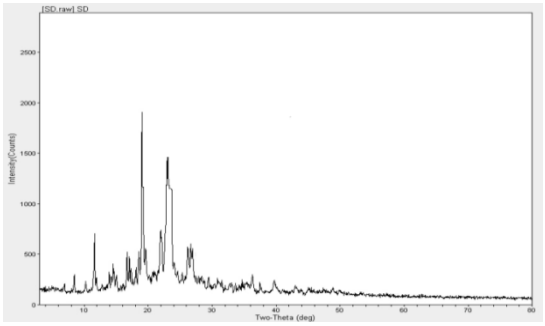

Figure. 3b. XRD spectrum for solid dispersion

2.13. Solubility Enhancement of Indomethacin using PEG 8000 by Solvent Evaporation method and Melting Method

Solid dispersions were prepared by using solvent evaporation and melting method at the ratios of 1:0.5, 1:1, 1:2, 1:3. From the percentage drug release data (fig. 4, 5) we can conclude that among the 8 formulations, S3 formulation by solvent evaporation method gave better drug release. Hence the better ratio was used for compression of tablets.

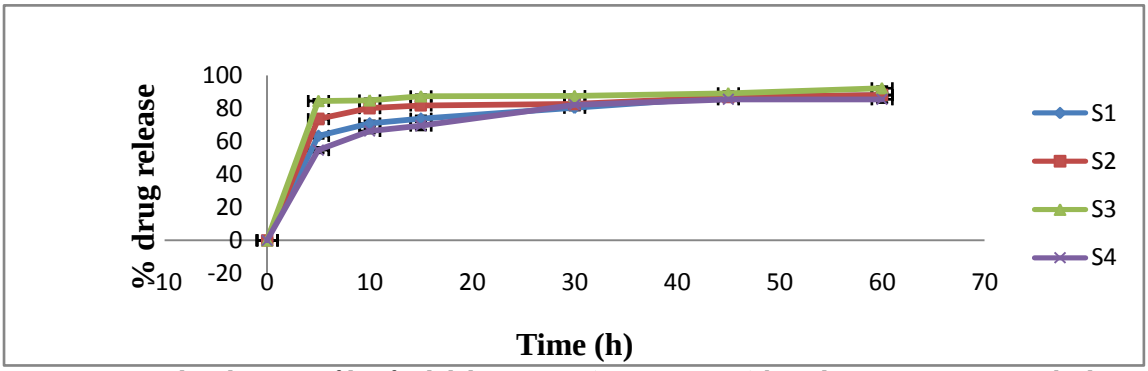

Figure. 4.*In vitro* dissolution profile of solid dispersions (S1, S2, S3, S4) by solvent evaporation method.

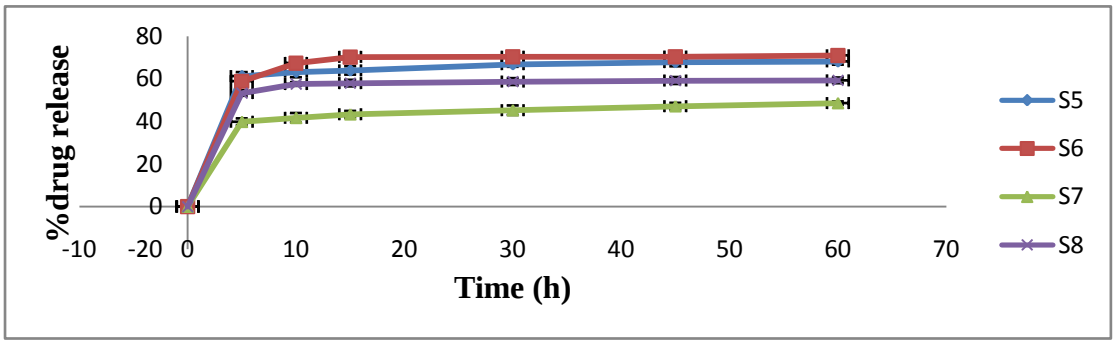

Figure. 5.*In vitro* dissolution profile of solid dispersions (S5, S6, S7, S8) by melting method.

2.14. Precompression Studies

All the precompression studies were performed in triplicate as per USP specifications. Bulk density and tapped density were found to lie in the range of 0.274-0.512 g/ml and 0.310-0.582 g/ml respectively. It was found that there is no major significant difference between bulk and tapped densities implying that the powders won't present any difficulty to get filled into the die cavity thereby making direct compression as the method of choice.

Angle of repose was found to lie in between 25°-31° and Carr's index was found to lie in the range 11.07-14.97 for all the formulations indicating good flowability and compressibility. Hausner's ratio was found to lie in the range of 1.12-1.31 indicating good flow properties. In order to improve the flowability of the powders, 2%w/w of glidant and 1%w/w lubricant were added. All the precompression parameters were tabulated in the Table No.4and were found to be in acceptable limits of USP (United States Pharmacopoeia).

Table No.4. Precompression Parameters

Formulation Codes	Angle of repose (°)±SD	Bulk density (g/cm3)±SD	Tapped density (g/cm3)±SD	Carr's index (%)±SD	Hausner'sratio± SD
F0	31±0.3	0.274±0.1	0.310±0.2	11.61±0.4	1.31±0.3
F1	29±0.1	0.512± 0.2	0.582±0.5	12.02±0.1	1.13±0.2
F2	29±0.3	0.444±0.5	0.512±0.4	13.28±0.2	1.15±0.1
F3	26±0.1	0.505±0.3	0.581±0.2	13.59±0.3	1.15±0.4
F4	27±0.2	0.389±0.6	0.439±0.3	11.38±0.4	1.12±0.5
F5	28±0.5	0.464±0.1	0.524±0.4	11.45±0.1	1.12±0.6
F6	26±0.2	0.283±0.2	0.325±0.1	12.92±0.6	1.14±0.3
F7	27±0.3	0.452±0.3	0.519±0.5	12.90±0.5	1.14±0.4
F8	28±0.1	0.289±0.5	0.325±0.3	11.07±0.2	1.12±0.1
F9	25±0.4	0.386±0.4	0.454±0.6	14.97± 0.3	1.17±0.5

Values are expressed as average standard deviation of n=3

Note: Formulations F0 was formulated without polymers, F1-F3 were formulated using *Moringa oleifera* gum and F4-F6 were formulated with HPMC K15 and F7-F9 were formulated by using Eudragit RL 100.

2.15. Post compression studies

Post compression studies were performed in triplicate as per USP specifications and the obtained results were found to be satisfactory and within the acceptable limits for the uniformity of weight (293-304 mg), hardness (6.13-6.5 kg/cm^2), thickness (3.47-3.56 mm), friability (0.44-0.58%) and content uniformity (95.32-99.96%). The hardness and friability values indicate that the tablets were having good mechanical strength so that can easily withstand possible wear and tear during handling. Content uniformity values indicate that the drug is uniformly distributed among all the batches. All the post compression parameters were tabulated in the Table No.5.

Table No.5. Post compression Parameters

Formulation Codes	Weight variation±SD	Friability (%)±SD	Thickness (mm)±SD	Hardness (kg/cm^2)±SD	Drug content (%)±SD
F0	300±1.75	0.53±0.1	3.51±0.09	6.25±0.13	99.45±1.1
F1	298±0.76	0.47±0.1	3.56±0.07	6.5±0.30	98.20±1.4
F2	299±0.98	0.58±0.2	3.47±0.07	6.42±0.25	96.34±1.2
F3	300±0.91	0.53±0.3	3.51±0.07	6.33±0.10	98.37±1.1
F4	295±1.53	0.44±0.1	3.47±0.05	6.28±0.10	98.92±1.5
F5	294±1.75	0.47±0.2	3.48±0.06	6.26±0.15	95.32±1.4
F6	296±1.60	0.48±0.3	3.51±0.04	6.22±0.15	99.54±1.7
F7	303±1.84	0.52±0.1	3.55±0.10	6.14±0.25	98.36±2.1
F8	293±1.74	0.51±0.2	3.48±0.07	6.13±0.10	99.96±2.1
F9	304±1.82	0.49±0.4	3.51±0.06	6.25±0.30	98.03±2.3

Values are expressed as mean ±SD, n=3.

Note: Formulations F1-F3 was formulated using *Moringa oleifera* gum and F4-F6 was formulated with HPMC K15 and F7-F9 were formulated by using Eudragit RL 100.

2.16. *In vitro* Dissolution Studies

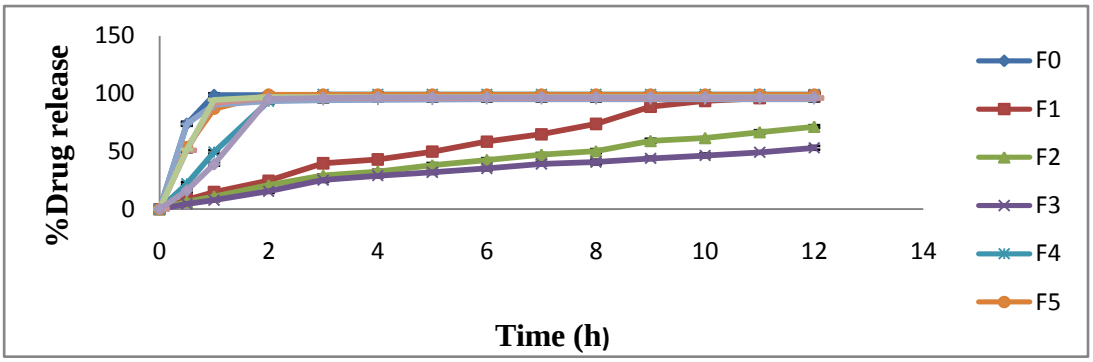

Figure. 6. *In vitro* dissolution profile of indomethacin from formulations F0-F9.

The formulations F1, F2, F3 were prepared by using 5%, 10%, 15% w/w of *Moringa oleifera* gum of the total weight of the tablet (300 mg) and the *in vitro* drug release was found to be 98.064%, 71.304%, 52.914% within 12 h respectively.

The formulations F4, F5, F6 were prepared by using 5%, 10%, 15% w/w of HPMC K15 of the total weight of the tablet (300 mg) and the *in vitro* drug release was found to be 99.276%, 98.862%, 94.98% within 3 h, 2 h, 6 h respectively.

The formulations F7, F8, F9 were prepared by using 5%, 10%, 15% w/w of Eudragit RL 100 of the total weight of the tablet (300 mg) and the *in vitro* drug release was found to be 96.192%, 96.972%, 96.684% within 2 h, 2 h, 4 h respectively.

From the release data it was found that formulation F1, F2, F3 sustained the release of the drug up to a period of 12 h when compared to F4-F9.The *in vitro* dissolution data for all the formulations F0-F9 was depicted in the fig. 6.From all the prepared tablets, it was concluded that formulation F1 had shown a better sustainable drug release from the dosage form 98.064% within 12 h.

2.17. Release Kinetics

The drug release data obtained were extrapolated by Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson- Crowell equations to find out the order and mechanism of drug release from these

formulations (Table No.6). The zero order plots of F1, F2, F3 were found to be fairly linear as the regression coefficient values are more toward one (0.960-0.986). This concludes that almost all the formulations follows zero order implying that the drug release from these formulations does not depend on the concentration of the drug. These are not sufficient to predict the kinetics, hence to confirm the exact mechanism of drug release from the tablets, the data were computed and graphed according to first order, Higuchi's equation, Hixson-Crowell equation and Korsmeyer-Peppa's equation.

F1, F2, F3 formulations followed zero order, Higuchi's equation, Korsmeyer-Peppa's, Hixson-Crowell equation and the diffusion mechanism from Korsmeyer-Peppa's was found to be Non-Fickian type. This may be due to the reason that the polymers employed in these formulations exhibited dominant diffusion pattern of release due to the formation of the gel layer around the tablet thereby retarding the release of the drug from the formulation.

The drug release kinetics concluded that F1 as the best formulation from the results and it states that the drug release from the dosage form follows Korsmeyer-Peppa's equation and Non -Fickian type of diffusion.

Table No. 6. Release Kinetics for Formulated Batches F0-F9

Formulation Code	Zero order plot		First order plot		Higuchi plot		Korsmeyer'sPeppas plot		Hixson Crowell plot	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	N	r^2	K
F0	0.254	3.771	0.103	0.071	0.477	19.13	0.467	0.061	0.216	-0.071
F1	0.986	8.314	0.145	0.147	0.966	30.49	0.998	0.793	0.959	-0.276
F2	0.983	5.689	0.021	-0.046	0.977	21.01	0.997	0.746	0.994	-0.122
F3	0.960	4.330	0.064	-0.080	0.982	16.22	0.989	0.780	0.980	-0.081
F4	0.546	6.597	0.419	0.285	0.765	28.92	0.752	0.414	0.593	-0.252
F5	0.362	4.651	0.253	0.158	0.605	22.28	0.614	0.146	0.414	-0.143
F6	0.273	3.710	0.009	0.018	0.499	18.59	0.645	0.061	0.444	-0.068
F7	0.329	4.365	0.041	0.046	0.565	21.18	0.516	0.139	0.307	-0.095
F8	0.321	4.351	0.058	0.055	0.554	21.19	0.496	0.135	0.279	-0.094
F9	0.541	6.729	0.157	0.131	0.747	29.28	0.746	0.501	0.496	-0.201

IV. CONCLUSION

From the results of the study, we can conclude that extracted gum *Moringa oleifera* exhibits good physicochemical properties. Enclosing solid dispersions containing indomethacin in polymer like *Moringa oleifera* gum by direct compression technique will help in achieving sustained release of the drug from the formulation. The advantage of sustained release solid dispersion is its monolithis structure that avoids the risk of burst release. Further it increases the effectiveness of the drug by localization of the drug at the site of action thereby reducing the dose required to be incorporated and in providing uniform delivery of indomethacin. The release of drug from sustained release solid dispersion is depends upon proper selection of carriers, molecular weight and concentration of carriers, drug polymer ratio, and appropriate mathematical models. The extracted and purified gum can be used as a release retardant for developing sustained release solid dispersions.

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