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Research Article

Formulation and Evaluation of Extended Release Pellets of NSAIDs Indole Derivatives.

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ABSTRACT
Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. The extended release products are formulated to make the contained medicament available over an extended period of time after administration within its therapeutic range and hence reduction in dosing frequency as compared to the conventional dosage forms. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain and inflammation caused by condition such as osteoarthritis, gout, ulcerative colitis, colon cancer. Aim of the present work is to formulate the Indomethacin pellets to present it in the form of capsules (Extended release pellets).To develop and over an extended period of time in the gastro intestinal track and compared the in-vitro dissolution profile with that of the marketed product.

KEYWORDS
Indomethacin, Extended Release Pellets

1. INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption [1]. Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the dosage form is complete, plasma drug concentration decline according to drug's pharmacokinetic profile. Eventually, plasma drug concentration fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate release dosage forms [2]. Dosage forms which can reduce at least a twofold reduction in dosing frequency as compared to the drug presented in a conventional form, such as solution or a prompt releasing conventional solid dosage form are termed as extended release dosage forms. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. The site-specific delivery of drugs to the colon has implications in a number of therapeutic areas, which include topical treatment of colonic disorders such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon and irritable bowel syndrome. Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. Because of their smaller particle size compared to single unit dosage forms these systems are capable of passing through the GI tract easily leading to low inter and intra subject variability [2, 3].

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain and inflammation caused by condition such as osteoarthritis, gout, ulcerative colitis, colon cancer. Its biological half-life is 4.5 hrs [4, 5].

When given conventionally it gets released in the upper GIT thereby causing irritation and ulcer in the upper GIT. The dosage form should be designed in such a way that it should minimize or prevent drug release in the acidic environment of upper GIT and start releasing the drug in a controlled manner once it reaches the alkaline environment of small intestine [6].

Aim of the present work is to formulate the Indomethacin pellets to present it in the form of capsules (Extended release pellets).To develop and over an extended period of time in the gastro intestinal track and compared the in-vitro dissolution profile with that of the marketed product. extended release pellet formulation of Indomethacin prepared by the centrifugation (rotary fluid bed granulation) or powder layering method for the first time, which provides a prolonged anti-inflammatory effect by ingestion of only one unit dose every 12 hours [7, 8].

2. MATERIALS AND METHODS

2.1.Materials

Indomethacin was obtained from Balaji drug supplier Surat, Gujarat, Hydroxypropyl cellulose was obtained from Subham pharma chem. Mumbai, Ethyl cellulose, Isopropyl alcohol from Merck (HPLC grade), Mumbai, Sodium lauryl sulphate, Povidone K-30, Talc and sugar spheres (500-600 mm) were purchased from Pragati chem. Impact PVT. LTD. Mumbai, All the chemicals used were of A. R. grade.

2.2.Methods

Pellets were prepared by Fluid bed processor (FBP). Preparation of drug layering solution was done by following procedure,

Isopropyl alcohol was taken into a suitable vessel and to it ethyl cellulose 4cps added, stirred well to get clear solution at room temperature. Purified water, sodium lauryl sulfate and hydroxy propyl cellulose were added to the above solution slowly under continuous stirring to dissolve completely. Then Indomethacin was added slowly under continuous stirring to get a uniform dispersion. After attaining uniform dispersion talc was added immediately with continuous stirring for not less than 30 min. The above dispersion was passed through #40 sieve and complete dispersion was passed. Dispensed sugar spheres were loaded into wurster column and the process started with present parameters to adjust the fluidization. The dispersion was sprayed onto sugar spheres at inlet temperature of 40±5°C and bed temperature of 35 ±5°C then spray rate increased slowly to optimum rate. The drug layered pellets was dried for not less than 15 min with low fluidization at a bed temperature of 40±5°C and weight gain was checked. The drug layered pellets were passed initially through #20 sieve and the twins retained on the sieve were removed. Again they are passed through #30 sieve and the passed drug layered pellets were discarded. The pellets were stored in suitable air tight container.

2.3. Extended release coating

Extended release coating solution was prepared with polymer concentration of 1:1 ratio (5%, 7% and 9%). Required quantity of isopropyl alcohol was transferred into a suitable vessel at room temperature to that ethyl cellulose 4 cps, purified water, and hydroxypropyl cellulose was added slowly under continuous stirring to dissolves completely. The drug layered pellets were loaded into wurster column and the process started with present parameters to adjust the fluidization. The solution was sprayed onto drug layered pellets at inlet temperature of 40±5°C and bed temperature of 35±5°C then spray rate increased slowly to optimum rate. The extended release coated pellets was dried for not less than 30 min with low fluidization at a bed temperature of 40±5°C and weight build up was checked the extended release coated pellets were passed initially through #20 sieve and the twins retained on the sieve were removed. Again they are passed through #30 sieve and the passed drug layered pellets were discarded.

2.4. Calibration curve of Indomethacin in 6.2 pH phosphate buffer

Drug (100 mg) was dissolved in 100 ml of methanol from this solution 5 ml was withdrawn and diluted to 100 ml with phosphate buffer pH 6.2. From the stock solution serial dilution were made to obtain the solution in concentrations ranging from 5-50 µg/ml. They were analyzed spectrophotometrically by measuring the absorbance at 319 nm.

Raw material analysis of Indomethacin was carried out using Fourier Transform Infra red spectrophotometer (FTIR) by KBr pellet method.

2.5. Particle size distribution of Indomethacin powders

The particle size measurement of indomethacin micronized powder was determined by using a (Mastersizer-2000) particle size analyzer. An appropriate amount of indomethacin powder was added into the analyzing chamber containing deionized water as the medium. A few drops of Triton solution (1% w/w) were added to disperse the powders. Test results of the type of powder were recorded. In addition, this powder was examined under a microscope with a magnification of 400X**.**

2.6. Evaluation of prepared pellets

2.6.1. Content uniformity

The content of one capsule was transferred into 200 ml volumetric flask; to it 100 ml equal volume of methanol and phosphate buffer (pH 6.2) was added. Then the solution was sonicated until then contents are dispersed and volume was made up with methanol and phosphate buffer (pH 6.2) in 1:1 ratio. This solution contains about 25 µg/ml indomethacin. Concomitantly the absorbance was determined 319nm, in spectrophotometer, using the methanol and pH 6.2 phosphate buffer mixture as the blank.

Content uniformity: $(TC/D)\ (A_U/A_S)$ --- (1)

T = labeled quantity of indomethacin in mg
C= concentration (µg per ml) in the standard solution
D= concentration (µg per ml) in the test solution
Based upon the labeled quantity per capsule and the extent of dilution Au and As are the absorbance of the solution from the capsule contents and the standard solution.

Weight variation, loss on drying, Bulk density, Tapped density, Carr's index and Hausner's ratio were done as per IP procedure. Loss on drying was measured by using Electronic loss on drying apparatus.

2.7. In-Vitro Drug Release Studies and Kinetic Modeling

In-vitro drug release studies of indomethacin were carried by using apparatus USP test-I rotation basket method with a stirring speed 75 rpm at 37 ± 0.5°C in 750ml of 6.2 phosphate buffers for 24 hours. 5 ml of sample withdrawn at interval of 1, 2, 4, 6, 12, 24 hours with the replacement of equal volume of dissolution media. The solution was filtered through Millipore HYLP filter and this filtrate was measured at 319 nm by UV spectrophotometer (UV-1700 SHIMADZU).

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi and Peppas. Based on the R & n value, the best-fit model was selected.

3. RESULTS AND DISCUSSION

3.1. Drug- Excipients compatibility study

Drug-Excipients compatibility study was carried out. From the preformulation studies, it was observed that mixtures shown have no color change.

When FT-IR Spectrum of indomethacin (pure drug) and optimized formulation of Indomethacin extended release pellets (F5) were compared, there were no major changes in the position of the spectrum. So it indicates absence of physical and chemical interactions of Indomethacin extended release pellets. It was shown in fig. 1.

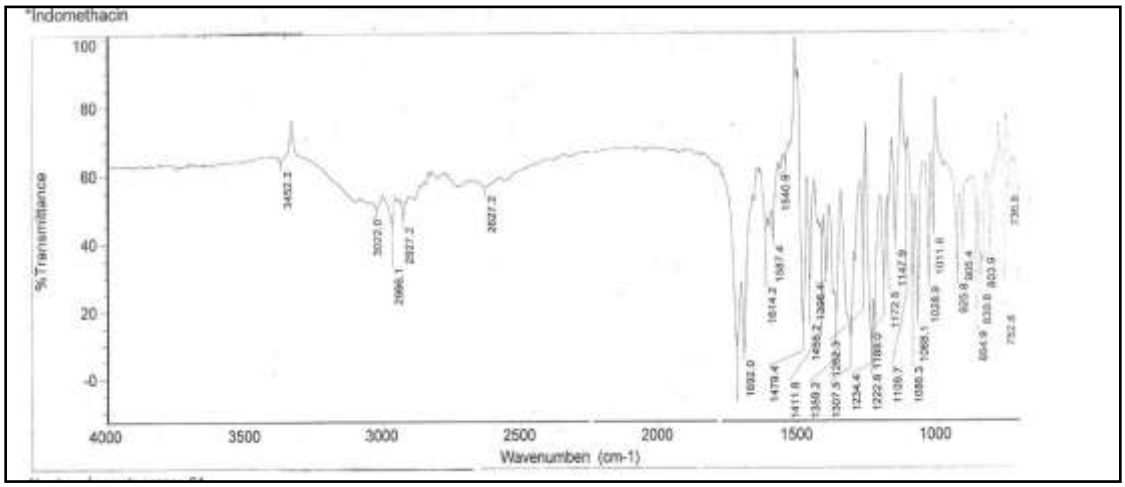

Fig. 1. FT-IR Spectrum of indomethacin (pure drug)

Interpretation of Indomethacin

Frequency	Groups assigned
3452.3	O-H Stretching
3022.0	C-H Stretching
1692.0	C=O Stretching
1455.2	C=C Stretching
925.8	C-H Stretching

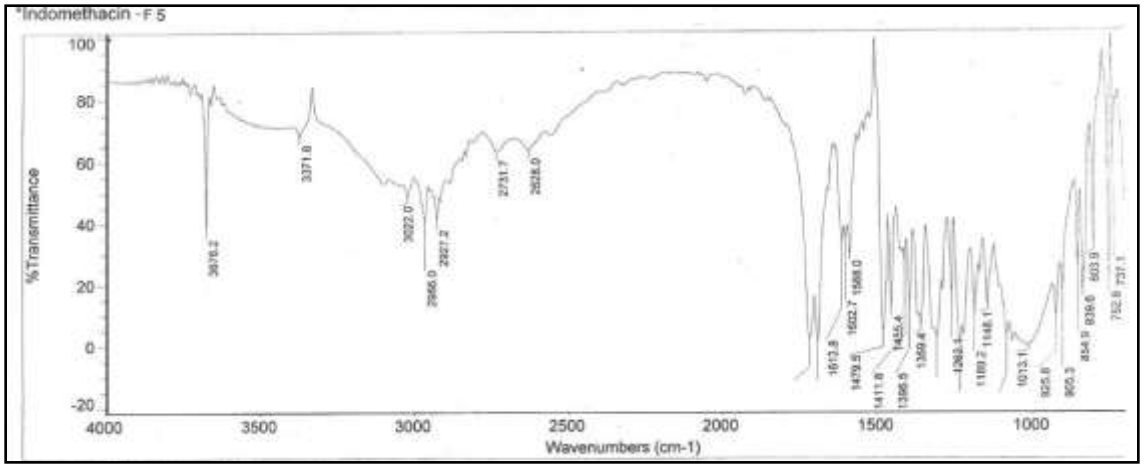

Fig. 2. FT-IR Spectrum of Formulation 5.

Interpretation F-5

Frequency	Groups assigned
3676.2	O-H Stretching
3022.0	C-H Stretching
1613. 8	C=O Stretching
1455.4	C=C Stretching
925.8	C-H Stretching

3.2. Bulk Density & Tap Density

The bulk density and tapped bulk density for all formulation varied in range of 0.821±0.011 to 0.873±0.014 and 0.873±0.019 to 0.918±0.008. The value obtained lies within the acceptable range and with no much difference found between bulk density and tapped bulk density.

3.3. Compressibility Index & Hausner's Ratio

The percent compressibility of pellets was determined by Carr's compressibility index. The percent compressibility for all formulation lies within the range of 6.01±1.57 to 6.209±0.63. Hausner's ratio was found to be in a range of 1.036±0.017 to 1.074±0.017 which shows good flow property.

3.4. Content uniformity

The results for uniformity of dosage units are presented in the table given below. The results were found to be within the limits (90 % to 110%). It shows that the drug was uniformly distributed.

3.5. Weight variation & Loss on drying

The weight of the capsule was fixed depending up the percentage of excipients used in the each formulation .Weight variation of the prepared capsules was within the limit .Mostly, the variation was within ± 7.5%. The prepared pellets of all the batches were evaluated for their moisture content. It is observed that the range around 1%.

3.6. Release Kinetics study for optimized extended release pellets

The tables and figures showed the correlation coefficient of different kinetic model for optimized (F-5) formulation. Higuchi plots were found to be of highest linearity with correlation coefficient greater than that of the zero order kinetics and correspond to that of the first order kinetics indicating that the drug release mechanism from these pellets by diffusion method. Studies revealed that release was found to be very close to zero- order kinetics with a value of 0.9796 indicating that the release was nearly independent of drug concentration. The in-vitro release was explained by higuchi model with a value of 0.9958 indicates a diffusion release. Moreover in-vitro release explained by korsmeyer- peppas equation also indicated a good linearity.

The in-vitro drug release profile of Indomethacin extended release pellets F5 formulation was shown in fig. The combination of ethyl cellulose and other polymers increases drug release rate due to a formation of a porous on the pellets. Formulation F-5 (containing ethyl cellulose 5% w/w and hydroxypropyl cellulose 9%w/w) showed better release profile as compared to other formulations i.e. very low initial drug release in the first two hrs and afterwards the rate of drug

release increased with almost complete release of the drug being achieved in 97.03% at 24 hrs respectively. Hence F-5 release profile was passed all USP test-1 limits.

4. CONCLUSION

The present work was carried out to design and evaluate Indomethacin capsules containing extended release pellets. Pellets technique using ethyl cellulose as the retardant has successfully extended the release of indomethacin from its pellets formulations. The in-vitro drug release profile of Indomethacin extended release pellets F5 formulation was shown in fig. The combination of ethyl cellulose and other polymers increases drug release rate due to a formation of a porous on the pellets. Formulation F-5 (containing ethyl cellulose 5% w/w and hydroxypropyl cellulose 9%w/w) showed better release profile. It was found that incorporation of hydroxypropyl cellulose in the pellets not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time and also it will act as suitable binding property.

Table 1. Formulation chart of Indomethacin pellets: Drug layering.

Sr. no.	**Name of Ingredients**	**Quantity per unit (mg)**					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	Indomethacin	75	75	75	75	75	75
2	Ethyl cellulose (4cps)	5	5	6	7	5	5
3	Povidone K30	20	-	-	-	-	-
4	Hydroxypropyl Cellulose, Low-substituted	-	20	-	-	-	-
5	Hydroxypropyl Cellulose	-	-	18	18	20	20
6	Sodium lauryl sulfate	0.5	0.5	0.5	0.5	0.5	0.5
7	Talc	1	1	1	1	1	1
8	Sugar spheres (500-600 µm)	217.5	217.5	217.5	217.5	217.5	217.5
9	Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
10	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2. Extended release coating.

Sr. no.	Name of Ingredients	Quantity per unit (mg)					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
11	Ethyl cellulose (4cps)	8	6	7	8	14	11
12	Povidone K30	8-	-	-	-	-	-
13	Hydroxypropyl Cellulose, Low-substituted	-	8	-	-	-	-
14	Hydroxypropyl Cellulose	-	-	6	8	11	14
15	Sodium lauryl sulfate	1	1	1	1	1	1
16	Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
17	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
18	Extended release pellet weight	336	336	336	336	336	336
19	Talc	1	1	1	1	1	1

Table 3. Evaluation of pellets of Indomethacin (physico-chemical characteristics).

Sr. No.	Bulk density (g/cc)	Tap density (g/cc)	Carr's Index (%)	Hausner's ratio
F-1	0.837±0.006	0.890±0.007	6.01±1.57	1.074±0.017
F-2	0.831±0.011	0.885±0.013	6.011±0.78	1.05±0.007
F-3	0.822±0.012	0.874±0.018	5.977±0.83	1.07±0.008
F-4	0.837±0.013	0.886±0.015	5.698±0.25	1.058±0.0005
F-5	0.845±0.012	0.899±0.008	6.209±0.63	1.049±0.030
F-6	0.873±0.014	0.918±0.008	4.866±0.73	1.036±0.017

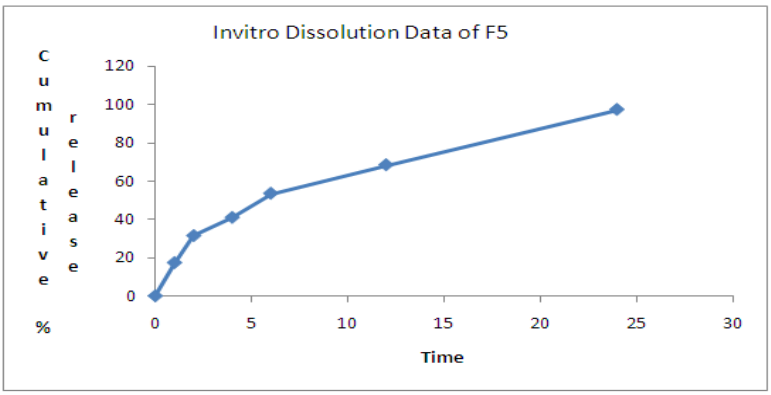

Fig. 3. Drug Release profile of Indomethacin extended release pellets F5 formulation.

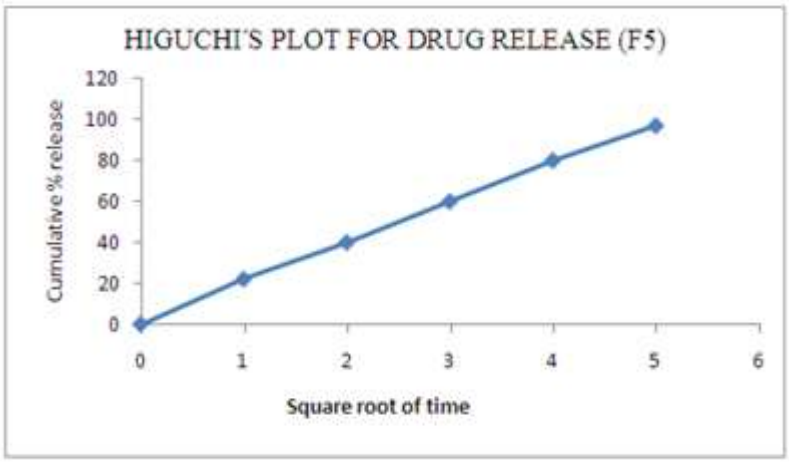

Fig. 4. Higuchi plot of F5 formulation.

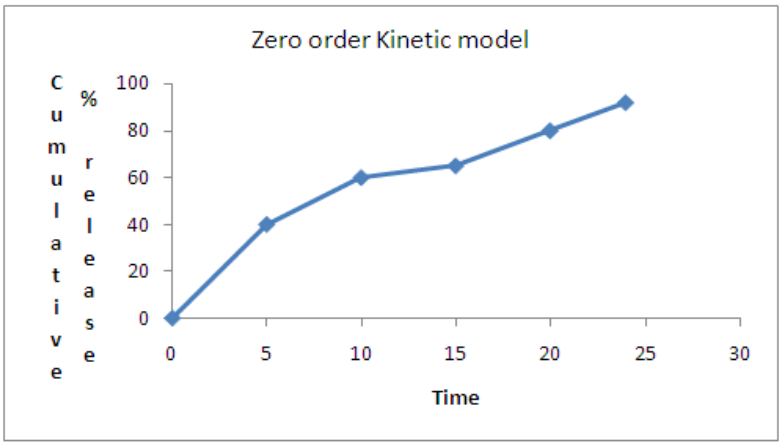

Fig. 5. Zero order kinetic model of F5 formulation.

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