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Original Article

FORMULATION AND EVALUATION OF INDOMETHACIN EXTENDED RELEASE PELLETS

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ABSTRACT

Objective: The present investigation was to design pellets loaded with Indomethacin for extended release. Indomethacin is a non steroidal anti inflammatory drug (NSAID) commonly used for reduction of pain and inflammation. To improve the bioavailability indomethacin was prepared by fluidised bed coating tablet technology.

Methods: Indomethacin pellets were prepared using hydroxy propyl methyl cellulose and ethyl cellulose as a polymer in different concentration. Pellets were evaluated for physico - chemical properties such as hardness, friability, thickness, weight variation, drug content uniformity and capsule lock length. *In vitro* drug release studies were carried out USP rotating basket type I method and the samples were analyzed at 319nm by UV spectrophotometer.

Results: FT-IR studies revealed that there was no interaction betweeen drug and polymers used in the study. The drug release from F5 formulation was found to zero order kinetic model. It was also found linear in higuchi plot which confirms that diffusion is one of the mechanism of drug release.

Conclusion: Among these formulations, Formulation (F5) containing Ethyl cellulose (4cps) 5mg & HPC 20 mg and extended release coating upto 7% showed optimized release pattern.The optimized formulation (F5) releases the drug upto 24hrs and fulfilled the requirements such as cost effective and high patient compliance.

Keywords: Indomethacin, Pellet technology, Zero order kinetic model.

INTRODUCTION

Indomethacin is a non-steroidal anti–inflammatory drug used in the symptomatic management of painful and inflammatory conditions such as rheumatoid arthritis and osteoarthritis. The most frequent adverse effects are gastro– intestinal (GI) and central nervous system disturbances [1].The traditional dosage forms of indomethacin such as tablets and capsules have to be taken three or four times per day. Most patients on this therapeutic regimen are elderly, often taking several other tablets or capsules per day for the treatment of other disease states, such as hypertension and depression. Accordingly, it is important to keep the number of unit doses per day at minimum in order to ensure patient's compliance to the particular therapeutic regimen. In addition, it is important, particularly in the treatment of rheumatoid arthritis, to maintain a constant antiinflammatory serum concentration of indomethacin. It is difficult to reach this goal by modifying the traditional dosage forms of indomethacin, as they are rapidly absorbed and provide high serum concentrations. Then, they are slowly metabolized and their serum concentrations fall down [2].These led to investigation of new dosage forms such as delayed release, extended release or enteric release formulations to minimize these symptoms. Intestinal complaints due to the conventional formulations of indomethacin capsules are rare [3] as they release the total content in the powder form, which disperses in the gastric fluid, avoiding any possibility of causing localized release as seen in the monolithic devices. Previous observations recommend continuous release indomethacin as an agent with relatively low rates of acute gastric mucosal bleeding.The advantage of controlled release capsules, it would be ideal to formulate this product as a multi-particulate system filled in capsules. There are various techniques for preparation of sustained release indomethacin, like microencapsulation, coating by use of Wurster column process, and preparing pellets by an extrusion /spheronization process [5].Wurster column process is one of the methods reported for production of indomethacin pellets [4-6].

Currently much emphasis has laid on multi-particulate dosage forms because of their multiple advantages over single unit dosage forms, like flexibility during formulation development and therapeutic benefits for the patients. These include increased bioavailability, predictable gastric emptying, and reduced risk of local irritation and systematic toxicity due to dose dumping [7,8]. The most attractive features of the powder layering system are the uniform distribution of the powder on cores and the high drying efficiency of the binder solution, as well as the easy-to-clean pan and possibility of applying the successive functional film coating using the same equipment. The critical aspects involved in the process of layering activated-surface powder using the aqueous binder solution are decreased adhesiveness of the binder on cores due to the presence of a wetting agent and the high latent heat of vaporization of water used as a binder vehicle [9-11].The objective of this study was to develop an extended release pellet formulation of indomethacin 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. This method was chosen because of the difficulty in managing the indomethacin powder with 1-3 mg in size and attractive features of the powder layering system. Further coating trials were undertaken to achieve a final formulation, meeting all the USP30 requirements. As recommended dosage for indomethacin extended release formulation is 75-150 mg daily [12], it was best suited to develop a 75 mg.

MATERIALS AND METHODS

Indomethacin was obtained from fabbrica Italiana sintetici, Itali. Hydroxy propyl cellulose was obtained from Hercules, china. Ethyl cellulose, Isopropyl alcohol, sodium lauryl sulphate, povidone k-30 were purchased from Merck, Mumbai. Talc and Sugar Spheres (500-600mm) was purchased from CDH (p) Ltd, New Delhi, India. All the chemicals used were of A.R. grade.

Methodology

Construction of standard curve for Indomethacin.

Indomethacin (100mg) was dissolved in 100ml of methanol from this solution 5ml was withdrawn and diluted to 100ml with phosphate buffer PH 6.2. Indomethacin is estimated spectrophotometrically at 319nm and it obeys beer-lamberts law in the range of 50mg/ml.

Preformulation studies

Performulation study is an investigation of physical and chemical properties of drug substance alone and in combination with excipients

Drug – Excepient compatibility studies

Pure drug and excepients in 1:1 ratio in glass vials were kept at various accelerated conditions in stability chamber. If there is no colour changes were selected for formulation development

FTIR study [Fourior transformer IR study]

Identification of pure and polymers were performed using Infrared Spectroscopy by KBR pellet method.

Particle size distribution of Indometnacin powder

It is estimated by using a Mastersizer-2000 particle size analyzer. Indomethacin powder was taken into the analyzing chamber containing deionized water as the medium. A few drops of triton solution was added to disperse the powders and the powder was examined under microscope with a magnification of 400x.

Formulation of Extended release pellets

Extended release pellets were prepared by Fluid bed processor.

Preparation of drug layering solution

Isopropyl alcohol was taken in a suitable vessel and added ethyl cellulose 4cps. Sodium lauryl sulphate, Hydroxy propyl cellulose and water were added to the above solution until it dissolves completely. Then Indomethacin was added slowly to form a uniform dispersion. Then it was passed through sieve 740 sugar spheres were loaded into wurster column and the dispersion was sprayed onto sugar spheres.

The drug layered pellets was dried with low fluidization at a bed temperature of 40 to 5c. The pellets were stored in suitable container.

Extended release coating

Extended release coating solution in which polymer concentration 1:1 ratio was prepared (5%, 7%, and 9%). Isopropyl alcohol mixed with ethyl cellulose 4cps, purified water, and Hydroxy propyl cellulose. This solution is used for extended release purpose.

The drug layered pellets were loaded into wurster columns the solution was sprayed onto drug layered pellets. The extended release coated pellets was dried at a bed temperature of 40 ±5°c. The talc was passed through #40 sieze and pellets were lubricated.

Table 1: Formulation chart of Indomethacin pellet

Ingredients	Quantity per unit (mg)					
	F1	F2	F3	F4	F5	F6
Indomethacin	75	75	75	75	75	75
Ethyl cellulose (4cps)	5	5	5	7	5	5
Povidone k30	20	-	-	-	-	-
Hydroxypropyl Cellulose, Low-substituted	-	20	-	-	-	-
Hydroxypropyl Cellulose	-	-	20	18	20	20
Sodium lauryl sulfate	0.5	0.5	0.5	0.5	0.5	0.5
Talc	1	1	1	1	1	1
Sugar spheres (500-600µm)	217.5	217.5	217.5	217.5	217.5	217.5
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Extended release coating

Ingredients	Quantity per unit (mg)					
	F1	F2	F3	F4	F5	F6
Ethyl cellulose (4cps)	8	8	8	8	11	14
Povidone k30	8	-	-	-	-	-
Hydroxypropyl Cellulose, Low-substituted	-	8	-	-	-	-
Hydroxypropyl Cellulose			8	8	11	14
Sodium lauryl sulfate	1	1	1	1	1	1
Isopropyl alcohol	qs	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs	qs
Extended release pellet weight	336	336	336	336	342	348
Talc	1	1	1	1	1	1

Evaluation of Pellets

The Properties of pellets such as weight variation, content uniformity and loss on drying were determined. Weight variation was performed according to IP procedure.

$$\text{weight variation} = \frac{(\text{capsule weight-Average weight})}{\text{Average weight of capsules}} \times 100$$

The drug content was determined by weighing 10 capsules individually and one capsule was transferred into 100ml equal volume of methanol and phosphate buffer PH 6.2 The solution was filtered and after suitable dilution its absorbance was measured at 319nm by UV visible Spectrophotometer [Shimadzu 1700]

Loss on drying was measured by using Electronic Loss on drying apparatus. Bulk density, Tapped density, Carr's index and Hausner's ratio were performed for Indomethacin pellets.

Invitro drug release studies

Invitro drug release of Indomethacin Extended release pellets was performed using USP Basket type apparatus [Electrolab TDT 08L-8 Basket dissolution apparatus] with a stirring speed 75 rpm at 37 t0.5c in 900ml of 6.2 phosphate buffer for 24 hours. Then 5ml samples were collected at 1 hour, 2 hour, 4hour, 6hour, 12 hour and 24 hours from midway between the surface of dissolution medium and the top of the rotating basket, not less than 1cm from the vessel wall and replace fresh buffer solution. After appropriate dilution and the Samples were analyzed at 319nm by UV Spectrophotometer.

Kinetic Modeling

The *invitro* release data was analyzed by the zero order kinetics equation as well as Higuchi's and Korsmeyer – Peppa's equation to understand the release profile and release mechanism. When a graph of the cumulative percentage of the drug released from the

pellet against time is plotted zero order release is linear in such a plot, indicating that the release rate is independent of concentration. The rate of release of the drug can be described mathematically as follows,

Rate of release = dcs/dt= k

CS= Concentration of the drug present in the matrix

t = time

k = rate constant

Hence to confirm the exact mechanism of drug release from the extended release pellets the data was computed and graphed according to Higuch's equation and korsemeyer peppa's equation

RESULTS AND DISCUSSION

The Compatibility between the drug and polymer was found to be good by these studies. From this study, it was observed that mixtures shown have no colour change.

FTIR Spectrum of Indomethacin & optimized formulation of Indomethacin extended release pellets were compared, there were no major changes in position of the spectrum it indicates the absence of physical and chemical interaction of Indomethacin extended release pellets.

The Bulk density, Tap density carr's Index and Hausner's ratio of Indomethacin extended release pellets were shown below the Table.

Table 3: Physico- chemical characteristics of indomethacin extended release pellets

Formulation code	Bulk density	Tap density(g/cc)	Carr's Index (g/cc)	Hausner's ratio
F-1	0.837±0.007	0.890±0.007	6.01±1.57	1.074±0.017
F-2	0.833±0.012	0.886±0.015	6.012±0.79	1.06±0.008
F-3	0.821±0.011	0.873±0.019	5.978±0.82	1.06±0.009
F-4	0.837±0.013	0.886±0.015	5.698±0.25	1.058±0.005
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

All these values are lies with in the range which shows good flow property. The content uniformity of Indomethacin extended release pellets were within the limits (90% to 110%). This shows that the drug was uniformly distributed Content uniformity and Capsule lock length were shown below the table.

Table 4: Content uniformity and Capsule lock length of Indomethacin extended release pellets

Formulation code	Content Uniformity	Capsule lock length in (mm)
F-1	99.1±0.73	19.30±0.10
F-2	99.4±0.95	19.33±0.09
F-3	100.9±0.66	19.35±0.10
F-4	98.3±1.05	19.31±0.09
F-5	100.7±1.19	19.33±0.11
F-6	99.5±0.92	19.23±0.12

Weight variation and loss on drying for prepared Extended release pellets were within the IP limit. Weight variation of all the extended release pellets was within the ± 7.5 Moisture content of the pellets were around 1%.

Table 5: Weight variation and loss on drying of Indomethacin extended release pellets

Formulation code	Weight (mg) ±SD	Loss on drying (%)
F-1	409±1.89	1.22±0.02
F-2	409±2.63	1.20±0.03
F-3	409±2.78	1.17±0.02
F-4	409±2.52	1.18±0.02
F-5	415±2.02	1.21±0.02
F-6	410±1.89	1.20±0.03

The i*nvitro* drug release profile of Indomethacin extended release pellets (F5) was shown in figure. The results indicated extended release of drug from all the formulations with increase in polymer concentration formulation (F5) composed of Ethyl cellulose (4cps) 5mg & HPC 20 mg and extended release coating upto 7% showed optimized release pattern.

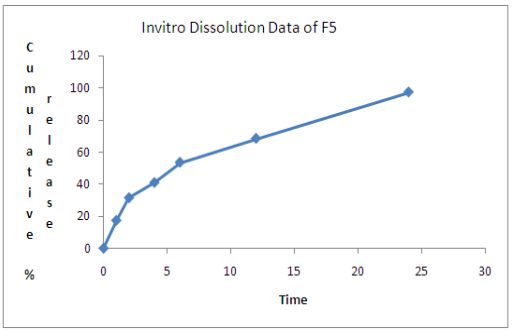

Fig. 1: Release profile of Indomethacin extended release pellets F-5 formulation

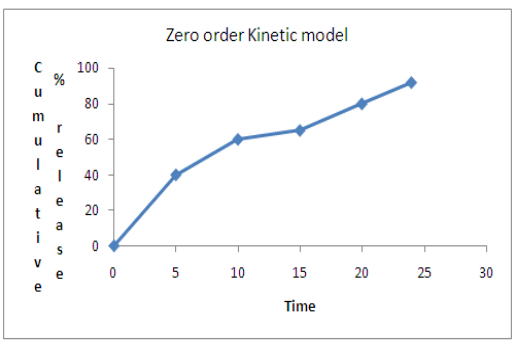

Fig. 2: Zero order kinetic model of F-5 formulation

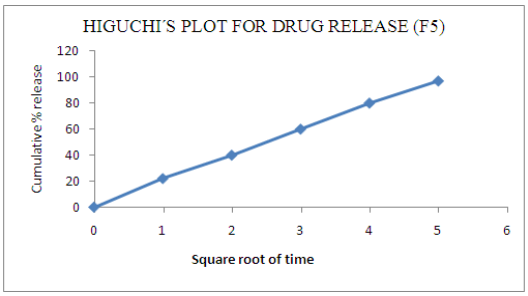

Fig. 3: Higuchi plot of F-5formulation.

CONCLUSION

The present research was carried out to develop a Indomethacin extended release pellets using ethyl cellulose and hydroxy propyl cellulose as a polymer. Formulation (F5) containing Ethyl cellulose (4cps) 5mg & HPC 20 mg and extended release coating upto 7% showed optimized release pattern. Pellets technique using ethyl cellulose as a retardant has successfully extended the release of indomethacin from its pellet formulation. The pellet formulation also reduced dosing frequency, increased bioavailability and provide better patient compliance.

CONFLICT OF INTERESTS

Declared None

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