

Formulation and in-vitro characterization of extended release pellets of indomethacin using powder-layering technique

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Abstract

The most frequent adverse effects of indomethacin like other NSAIDs are gastro-intestinal and central nervous system disturbances. Extended release or enteric release formulations minimize these symptoms. 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. Layered, nonpareil pellets composed of sugar, Avicel PH 101 and lactose were prepared using FREUND CF-granulator and were treated by a binder solution (HPC-L) applied by spray gun. A conical designed powder-feeding unit applied the drug powder. Drug content of pellets was determined by HPLC method. Eudragit NE 30 D was used for coating the prepared pellets. The results show that increasing the amount of Eudragit NE 30 D, Opadray and SDS in coating solution adjusts release of the pellets. The dissolution profile achieved from pellets containing 500 g nonpareil, 400 g indomethacin, 400 ml HPC 8%, 61g talc, 50 g Opadray[®] and coating consisted of 37.5 g Eudragit NE 30 D, 1.8 g SDS, 7.5 g Opadray[®] passed USP30 standards for indomethacin release and was comparable with retard Indocid[®]75 Capsule from MDS company.

Keywords: Indomethacin; Pellet; Extended release; Powder-layering technique

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 anti-inflammatory 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.

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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 (2). To have 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 (4-6). Wurster column process is one of the methods reported for production of indomethacin pellets (5). Pellets are prepared by spraying slurry of indomethacin, Eudragit® S100, dibutyl sebacate and alcohol on an appropriate mesh fraction of nonpareil seeds. The particle size of indomethacin (1-30 µm) and nonpareil (590-710 µm) is important for improving properties of indomethacin sustained release pellets (5).

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 µm 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 formulation designed for release in 12 h, so that the prescribed dosage can be 1 to 2 capsules daily.

MATERIALS AND METHODS

Materials

All the materials used for the formulation trials complied the pharmacopoeias requirements and were all from analytical grades.

Indomethacin (Behdashtkar, Iran), Microcrystalline cellulose PH 101 (JRS Pharma, Germany), Lactose monohydrate (Meggle, Germany), Sucrose (Khalij, UAE), Polyvinyl pyrrolidone (PVP-K30) (ISP, USA), Hydroxypropyl cellulose (HPC-L) (Nippon Soda, Japan), Eudragit NE 30D (Rohm GmbH, Germany), Talc (IL SHIN, South Korea), Sodium dodecyl sulfate (SDS) (Merck, Germany), Opadray® (Colorcon, UK) (Containing

Table 1. Studied formulations of extended release indomethacin pellets

Indomethacin Pellet				Coating ingredients/500g pellets				
Formulation code	Nonpareil Seeds (g)	Indomethacin powder (g)	HPC (ml)	Talc (g)	Opadray® (g)	Dispersion of Eudragit NE 30 D (g)	SDS (g)	Opadray® (g)
IHE 1	500	250	590 ml 8%	50	---	12.5	---	---
IHE 2	500	220	590 ml 8%	42	36	15	---	---
IHE 3	500	220	590 ml 5%	42	36	25	---	---
IHE 4	500	220	590 ml 5%	42	36	31.5	---	---
IHE 5	500	220	590 ml 5%	42	36	37.5	---	---
IHE 6 O	500	400	400 ml 8%	61	50	37.5	---	7.5
IHE 6 S	500	400	400 ml 8%	61	50	37.5	1.8	---
IHE 6 SO	500	400	400 ml 8%	61	50	37.5	1.8	7.5

hypromellose 6cp (USP), PEG 400 (NF), PEG 8000 (NF)).

Preparation of Indomethacin pellets

Layered pellets were prepared using FREUND CF-granulator (Japan). Nonpareil spheres composed of sugar, Avicel PH 101 and lactose (mesh 25-30) (1:1:1) prepared by powder layering method were poured into the coating pan, and were treated by a binder solution of HPC-L 10% that was applied by spray guns. The drug powder containing indomethacin, talc and magnesium stearate (8:1:0.1) was applied by a conical designed powder-feeding unit and were treated by a binder solution of HPC-L in different concentration shown in table 1.

The process conditions were as follows: the rate of powder feeding about 10 g/min, the weight ratio of powder to nonpareil seeds 1:1, the pan speed 200 rpm, preheating the cases to 34-35 °C, and fluidizing airflow 71-80 m³/h. Table 1 shows the constituents of various studied formulations.

Drug content measurements

Determination of indomethacin content of pellets was carried out by an HPLC method described in USP30 (13). Mobile phase was prepared by a mixture of methanol, water, and phosphoric acid (600:400:8), and filtered through a membrane filter of 0.45 µm (Millipor,

Ireland). 10 ml of phosphoric acid was diluted with water to make 1000 ml of solution. To prepare standard indomethacin preparation, 40 mg of USP Indomethacin RS, was accurately weighed, transferred to a 50 ml volumetric flask, and was dissolve in 30 ml of acetonitrile. It was diluted with diluted phosphoric acid to volume, and was mixed. For preparation of Assay solution, the contents of 20 capsules were weighed and finely powdered. An accurately weighed portion of the powder, equivalent to about 75 mg of indomethacin, was transferred to a 100 ml volumetric flask, 40 ml of diluted phosphoric acid was added, and shaken for 1 hour. 40 ml of acetonitrile was added, mixed, diluted with acetonitrile to volume, and mixed. A portion of this solution was centrifuged and the supernatant liquid was filtered through a filter having a porosity of 0.45 µm. The filtrate was used as the assay preparation. Chromatographic system: The liquid chromatograph was equipped with a 240 nm UV detector and a 4.6 mm × 250mm cartridge column Novapack packing L1 4/µm. The flow rate was about 2 ml per minute (13).

Coating the indomethacin pellets

Eudragit NE 30 D was used for coating 500 g of the prepared pellets. Table 1 shows the ingredients of the coating suspension.

The coating was carried out using the same CF-granulator pan by means of a constant and homogeneous one-way airflow into the core bed combined with a suitable spraying system for the coating material. The process conditions for coating were as follow: spray rate 2.2 g/min, product temperature 37 °C, pan speed 200 rpm, nozzle diameter 1 mm, and spray air pressure 2 bars. To improve the dissolution profile of the indomethacin pellets and to attain uniformity in the drug release, 0.25% SDS was added to the coating suspension.

Characterization of coated pellets

Extended release pellets of indomethacin were filled in hard gelatin capsules according to the assay of final coated pellets. Drug release rate from coated pellets was determined according to the USP30 paddle method, the stirring rate was 75 rpm and the dissolution medium was phosphate buffer solution pH 6.2 (12).

At predetermined time intervals, 5 ml samples were withdrawn and analyzed for drug released by HPLC method. Each time the dissolution medium was replaced with fresh buffer solution. USP30 standards for sustained release indomethacin capsules are: 1h: 12-32%, 2h: 27-52%, 4h: 50-80%, 12h:>80%

Dissolution efficacy (DE) and mean dissolution time (MDT) were used to translate the profile differences into single values (14). $DE_{12\%}$ is defined as the dissolution efficacy percentage up to 12 hr of dissolution test:

$$DE\% = \frac{\int_0^t Y dt}{y_{100} \times t} \times 100 \quad \text{eq. [1]}$$

MDT is a measure of the dissolution rate: the higher the MDT, the slower the release rate

$$MDT = \frac{\sum_{i=1}^{i=n} T_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad \text{eq. [2]}$$

Where i is the dissolution sample number, n is the number of dissolution sample time, T_{mid} is the time at the midpoint between i and $i-1$ and ΔM is the amount of drug dissolved between $i-1$ and i . The similarities between two dissolution profiles were assessed by similarity factor (f_2).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^{n-1} (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\} \quad \text{q. [3]}$$

Where n is the number of pull points, R_t is the reference profile at time point t , and T_t is the test profile at the same time point (14,15).

Film casting studies

Five ml of Eudragit NE 30 D dispersion (the same formulation as used for coating, IHE6SO) was also transferred into Petri dishes and dried at hot air oven for 2 h. The dissolution medium was poured in the Petri dish to cover up the complete film and then left in ambient condition for 2 h with slight periodic swirling. The buffer was poured out and the films were observed under microscope for probable cracks or apparent defects.

Statistical analysis

All tests were performed in triplicate and results reported as mean \pm standard deviation. One-way analysis of variance (ANOVA) test was used to determine statistical differences; the significance for all tests was at $P \leq 0.05$.

RESULTS

As Fig. 1 shows, the release in IHE3 decreased consistently to pass the USP standards.

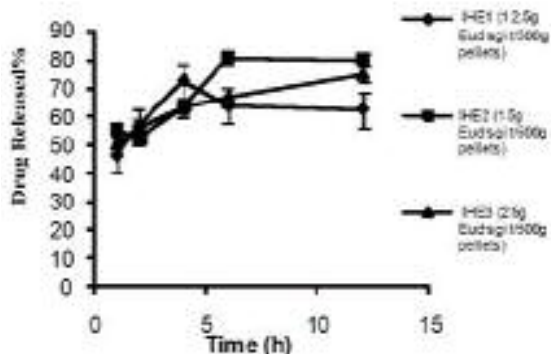


Fig. 1. Effect of Eudragit NE 30 D content on drug release from indomethacin pellets in phosphate buffer solution (pH=6.2) (n=6).

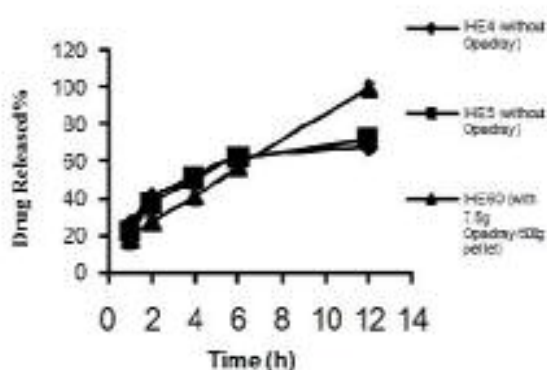


Fig. 2. Effect of addition of Opadray[®] on drug release from indomethacin pellets in phosphate buffer solution (pH=6.2) (n=6).

As Table 1 shows the amount of indomethacin powder, Opadray[®] and talc in formulations of IHE6O, IHE6S, IHE6SO was increased with respect to the other formulations. The amount of Eudragit NE 30 D was increased in IHE6O, IHE6S and IHE6SO and SDS was added to coating solution of IHE6S and IHE6SO. Opadray[®] was included in coating solution of IHE6O and IHE6SO. Considering these changes in formulations, Table 2 shows that recovery or percentage of indomethacin remained on the nonpareil with respect to the first amount improved in IHE3, IHE4, IHE5. Formulations IHE6O, IHE6S, IHE6SO also got better and the uniformity of powder layering was improved.

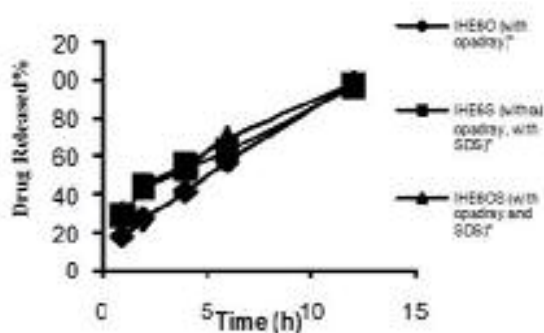


Fig. 3. Effect of addition of Opadray[®] and SDS on drug release from indomethacin pellets in phosphate buffer solution (pH= 6.2) (n=6).

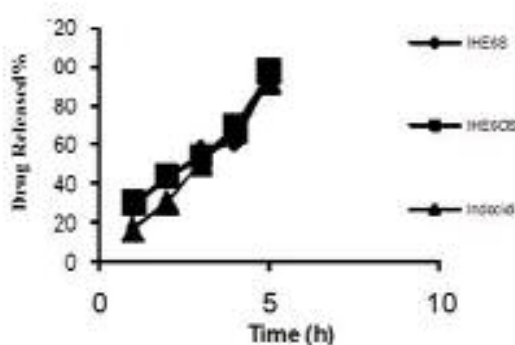


Fig. 4. Comparison of dissolution profiles of prepared indomethacin pellets (RAHA) and Indocid (MSD) in phosphate buffer solution (pH=6.2) (n=6).

Fig. 3 shows that in IHE6O formulation the release in last sampling time was near the standard of USP but in other times was lower than that. However, IHE6S and IHE6OS were in accordance with USP standards in all the sampling times.

Fig. 4 compares the release of Indocid as the reference capsule and IHE6S and IHE6OS. As this figure indicates, the dissolution profiles of IHE6S and IHE6OS are similar to Indocid capsules.

DISCUSSION

The aim of this study was to develop an extended release formulation of indomethacin meeting all the USP30 specifications. The ratio of the indomethacin to the

excipients was 75 mg to 150 mg blends of excipients per capsule. Powder layering process led to the formation of multiple layers of drug particles that adhere to one another due to capillary pressure and interfacial forces originating from the liquid phase, allowing the enlargement of the initial cores (16). It should be noted that, the process of powder layering could be continued until reaching the desired particle size. After each wetting powder cycle, intra particular solid bridges are formed by complete removal of water by stream of warm air blown through the perforated sword system in the equipment. Different polymers can further produce films on the final pellets in order to obtain multi-particulate dosage forms with extended release properties (17,18).

In order to maximize the interactions between drug and inert cores a micronized indomethacin powder with a mean diameter of 300 μm was chosen. The finer the powder, the higher the yield of pellets (5). Flow of powder is an important variable in this method. Indomethacin powder is characterized by scarce flow-ability. To overcome this problem, talc was employed as a flow activator. In order to promote the pellet separation into distinct units, 15-19 w/w% talc was added to the drug powder as efficient anti-sticking and gliding agents to guarantee sufficient flow of the powder. Unfortunately, the addition of talc did not completely solve the stickiness problem, so Opadray[®] was used which improved the results.

The results of assay before coating the pellets showed that increasing the weight of indomethacin powder near to the weight of nonpareils increased the drug loading in the pellets.

Reducing HPC in the binder solution from 8% to 5% decreased the viscosity of the binder solution and produced pellets with smoother surface. However, in final formulation (IHE6SO) for improving the recovery (percentage of indomethacin remaining on the nonpareils with respect to the first amount) of pellets, HPC concentration was increased again while less smooth surface was obtained (Table 2).

A study on preparation of ibuprofen pellets showed that the use of a more dilute binder solution and the presence of talc as an anti-sticking agent resulted in the separation of each pellet into individual units during the layering process (18). The formulations with less viscous and sticky binder (an aqueous solution of 7% w/w of PVP-K 30) produced a relatively smooth surface and homogeneous morphological characteristics but caused pellets with seedless drug particles and lower recovery. This problem was tentatively attributed to the too low adhesion capacity of PVP (compared to HPC) that led to the formation of small-dispersed particles and formation of seedless drug aggregates (18).

The results of sieve analysis showed 92% of pellets were between mesh 16 and 18 or between 14 and 16. Pellets were

Table 2. Effect of formulation on recovery percentage, size of pellets and drug contents.

Formulation	Recovery (%)	Size of pellets (mm)	Drug contents of pellets \pm SD (mg/150 mg)
IHE 1	20	1-1.18	75 \pm 0.1
IHE 2	20	1-1.18	75 \pm 0.1
IHE 3	24	1-1.18	75 \pm 0.2
IHE 4	24	1-1.18	75 \pm 0.1
IHE 5	24	1-1.18	75 \pm 0.1
IHE 6 O	33	1.18-1.4	75 \pm 0.08
IHE 6 S	33	1.18-1.4	75 \pm 0.07
IHE 6 SO	33	1.18-1.4	75 \pm 0.07

subjected to a film coating process using Eudragit NE 30 D in order to produce a sustained release formulation. Coating the pellets caused 2% overweight. The results of the drug release study of the coated pellets filled in size 2 capsules indicate that except formulations of IHE6S and IHE6SO none of the pellets could achieve the desired standard requirements of drug release profile of USP30.

Pellets of IHE1 were not spherical and smooth, they were sticky and their recovery was low. After coating, these pellets were quite sticky and did not pass the standards of USP release test.

Thus in pellets of IHE2 Opadray[®] were added as anti-sticking agent which improved the surface of pellets. They became smooth, spherical and separated from each other. The dissolution profile of pellets in presence of Opadray[®] is seen in Fig. 2.

Although slight improvement was seen but the initial release was still high. Increasing Eudragit NE 30 D as much as 66% w/w in formulation IHE3 was also not effective. However, increasing its percentage in batch IHE4, IHE5 was effective to decrease the initial release and bring it nearer to the standards of USP30. However, still the amount of drug released after 12 hr did not meet the USP standards (Fig. 2). This was related to the stickiness of pellets in dissolution medium. Thus Opadray[®] was used to separate multi-particulates that improved the release of the final sample to near 100 % but drug release of other samples decreased lower than the USP standard (Fig. 3). SDS was used as a pore-forming agent in the coating of pellets to improve drug release according to the USP30 standards. In a previous study pore former hydroxy propyl methyl cellulose, lactose, polyethylene glycol (PEG) and polyvinyl pyrrolidone (PVP) were released at the beginning of the release process. The rate and extent of water uptake of the polymeric films were

much higher in phosphate buffer pH 6.8 than in pH 5.0 and the concentration of pore former had a significant influence on the permeability to water vapour (19). In another report, Eudragit L-100 that is soluble in the intestinal pH has been used as the pore-former in combination with Eudragit S100 (20).

The maintenance of the desired drug release profile from the micro porous membrane system containing SDS at accelerated conditions was further studied through the casted films on Petri dishes.

Dissolution profiles of pellets of formulations IHE6S and IHE6SO are shown in Fig. 4 that are comparable with retard Indocid[®]. The results of dissolution efficiency ($DE_{12\%}$), mean dissolution time (MDT) and similarity factor (f_2) for batches that pass the standards of USP30 are shown in Table 3.

Comparing the MDT and $DE_{12\%}$ of pellets in different formulations showed that increasing the amount of Eudragit NE 30 D increases MDT (Table 3). As it can be seen in this Table, $DE_{12\%}$ for pellets IHE2 and IHE3 and MDT for pellets IHE3 is high but statistical analysis of data showed that the difference of $DE_{12\%}$ of pellets IHE3 and IHE5 is significant ($P \leq 0.05$). However, non of them did pass the standards of USP30 specially in the first 2 hours of release test.

Addition of SDS to pellets IHE6S and IHE6OS causes acceptable f_2 in relation to Indocid[®]. This can be explained by the fact that the soluble salt of SDS in contact with the dissolution medium continues to dissolve and provide the required micro pores in the polymer membrane and maintains the release profile. Secondly, SDS released into the dissolution medium will also help in dissolving the indomethacin (8). The results of release test of these two formulations are similar to retard Indocid 75 (MSD).

Comparing MDT and $DE_{12\%}$ of 3 pellet formulations IHE6O, IHE6S, IHE6OS

Table 3. Release parameters of indomethacin from different formulations (n=3) (MDT: mean dissolution time, DE_{12%}: Dissolution efficiency up to 12 hours of release test and f₂: similarity factor)

Formulation code	MDT (hr) ± SD	DE _{12%} ± SD	f ₂
IHE1	2.4 ± 0.2	63.3 ± 4.66	
IHE2	4.4 ± 0.2	67.34 ± 1.27	
IHE3	5.0 ± 0.3	60.64 ± 3.6	
IHE4	3.8 ± 0.8	52.3 ± 1.02	
IHE5	4.1 ± 0.3	46.4 ± 11.8	
IHE6O	6.2 ± 0.2	54.46 ± 1.2	
IHE6S	5.9 ± 0.16	53.68 ± 12.75	50.7
IHE6OS	5.7 ± 0.06	63.2 ± 0.9	50
Indocid [®] retard(MSD)	5.2 ± 0.4	58.5 ± 3.8	

show that SDS and Opadray[®] increase MDT and DE_{12%}. It seems that separating the multi-particulates and preventing their agglomeration in dissolution medium cause increasing MDT and DE_{12%}.

CONCLUSION

Extended release capsules of indomethacin were designed using powder-layering technology and the retardation of the release rate was achieved through coating the pellets with Eudragit NE 30 D, SDS and Opadray[®]. The dissolution profile achieved from pellets containing 500 g nonpareil, 400 g indomethacin, 400 ml HPC 8%, 61 g talc, 50 g Opadray[®] and coating of 37.5 g Eudragit NE 30 D, 1.8 g SDS, 7.5 g Opadray[®] passed USP30 standards for indomethacin release. Therefore it would be possible to maintain a constant anti-inflammatory serum concentration of indomethacin by ingestion of only one unit dose every 12 hours, and reduce the gastrointestinal disturbances.

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