Design and Evaluation of Chronomodulated Delivery of Indomethacin Tablets for Rheumatoid arthritis

Tatikayala Ravikumar[1], Golla Chandramouli[2], Radapaka Avinash[3]
[1,2,3]*Chaitanya Institute of Pharmaceutical Sciences, Rampur, Hanamkonda*

Abstract **- The main objective of the present work is to design chronomodulated tablets of indomethacin by compression method. The press-coated tablet containing indomethacin in the inner core was formulated with an outer layer by varying ratios of both hydrophobic and hydrophilic polymers such as Eudragit RL 100 and HPMC K 100M. The prepared core and press-coat tablets were evaluated parameters like weight variation, hardness, thickness, friability, disintegration, core erosion test, and in vitro release studies. The release pattern of the press-coated tablet exhibited a period without drug release (lag time, 4hrs) followed by a rapid and complete release of the drug. The formulation (F3) core tablet showed 97% of drug release in 1 hr, whereas the press-coated formulation (F6) exhibits 97.64% in 6 hrs.**

Index Terms **- Indomethacin, Eudragit RL100, HPMC K100M, and Arthritis.**

1.INTRODUCTION

Pulsatile drug delivery systems are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged period [(1)]. The pulsatile release is exploited to target proximal and distal colonic regions via the oral route based on a time-dependent strategy [(2)].

The concept of press coated technique, in which the core tablet is compression coated with different concentrations of polymers. When this tablet comes in contact with the stomach fluids it produces a lag time of drug release up to 6 hrs, after lag time the core tablet contains super disintegrant, the tablet disintegrates in few minutes and burst release of drug present in it [(3)]. To formulate and evaluate an oral drug delivery system of indomethacin intended to approximate the chronobiology of arthritis. It is a chrono-pharmaceutical for better treatment of early morning stiffness and symptomatic relief from pain in patients with rheumatoid arthritis.

2. MATERIALS AND METHODS

2.1. Materials

Indomethacin was chosen as a model drug obtained gift sample from Meenaxy Pharma Pvt Ltd, Hyderabad. Polymers like HPMC K100 and Eudragit RL 100 were procured from Merk Pvt Ltd. Avicel PH 101, Dicalcium phosphate, Crospovidone, Talc and Magnesium stearate were procured from Apurva inorganics Ltd. All the chemicals used in the study were of analytical grade.

2.2. Methods

Preparation of indomethacin press-coated tablets

Preparation of indomethacin core tablets

Accurately weigh all the ingredients and mix thoroughly by using a motor and pestle and the pre-weighed amount of formulation was direct compressed using a tablet punching machine. The components are listed in Table 1.

Table 1: Formulation design of indomethacin core tablets

Ingredients	Formulations of core tablets		
	F1	F2	F3
Indomethacin	100	100	100
Avicel PH 101	30	35	40
Dicalcium phosphate	25	35	45
Crospovidone	15	20	25
Talc	05	05	05
Magnesium stearate	05	05	05
Total weight of core tablet (mg)	180	200	220

Preparation of press-coated tablets of indomethacin

Press coated tablet is a system in which the surface of an inner core is surrounded by the coat. These coats prevent drug release from the core until the polymeric coat is entirely eroded, and dissolved. In the process of compression, the coating is half the quantity of outer coating material transferred into the die and the core tablet was placed manually in the center of the die and pressed a little bit to fix the lower part of the coating material. Then the remaining half quantity of outer coating material was added to the die and compressed using a rotary tablet punching machine [(4)]. The components are mentioned in Table 2.

Table 2: Formulation of press-coated tablets of indomethacin

	Press-coated indomethacin formulations					
Ingredients	F1	F2	F3	F4	F5	F6
Core tablet (Drug)	220	220	220	220	220	220
HPMC K 100 M	25	30	35	15	20	25
Eudragit RL 100	15	20	25	25	30	35
Avicel PH 101	40	30	20	40	30	20
Total weight of tablet (mg)	300	300	300	300	300	300

2.3. Evaluation of core and coated tablets

Weight variation

Randomly selected 20 tablets of each formulation batch were weighed using an electronic digital balance and the test was performed according to the Indian Pharmacopeia.

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using vernier calipers.

Hardness test

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness each was recorded in kg/cm^2 and the average hardness and the standard deviation were reported [(5)].

Friability test

The six (6) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25rpm for 4min (100 rotations) in the Roche friabilator [(6)].

Drug content determination

Ten core tablets were weighed, triturated, and powdered. Powder triturated equivalent to the average weight of the tablet was weighed and transferred to a 100 ml volumetric flask. Initially, about 50 ml of methanol was added and the flask was shaken thoroughly and the volume was made up to 100 ml with the methanol. The resulting solution was diluted suitably and the drug content was estimated spectrophotometrically at 320 nm [(7)].

Core erosion test

Compression-coated tablets were separately immersed in the Petri plate containing 7.4 pH Phosphate buffer at 37ºC for 3 hrs. After the tablets were removed from the medium, the gelated portion of the outer layer and the dissolved or gelated portion of each core tablet was carefully removed to obtain the non-eroded residual core. The dry mass of each non-eroded residual core was measured after drying for 20 hrs at 40ºC. The initial mass of each core tablet and the mass of each non-eroded residual core were used to calculate the core erosion ratio [(8)].

In-vitro drug release studies

Drug release studies were carried out using USP type II dissolution test apparatus, and the rotating paddle method. The study was conducted at 37±0.5ºC and 50 rpm using 900 ml of 1.2 pH buffer for 2 hrs followed by 7.4 pH buffers until completion of the studies. Aliquots of the sample (2 ml) were withdrawn at regular pre-determined time intervals, diluted suitably and the drug content was measured spectrophotometrically at 320 nm [(9 & 10)].

3. RESULTS AND DISCUSSION

Preparation of indomethacin core tablets

Indomethacin core tablets were prepared by super disintegrant like crospovidone by direct compression technique using 8mm dies and punches in a tablet punching machine. Here developing three formulations of core tablets in that formulation (F3) are considered optimized core tablets of indomethacin. The study was based on disintegration time with different concentrations of super disintegrants such as crospovidone. The results are shown in Figure 1.

Figure 1: Photographs showing (A) core tablet and (B) press-coat tablet of indomethacin

Evaluation of core tablets

The core tablets were evaluated for the following parameters like weight variation, hardness, thickness, friability, and drug content. In those formulations, F3 requires less time to release the drug from the core tablet. The results of core tablets are shown in Table 3.

Table 3: Evaluation of core tablets

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (Kg)	Friability (%)	Disintegration time (Sec)	Drug content (%)
F1	180.30 ± 3.75	2.94 ± 0.4	2.7 ± 0.5	0.38	30	92.8 ± 1.5
F2	200.15 ± 3.96	3.16 ± 0.6	2.9 ± 0.3	0.35	26	94.51 ± 2.8
F3	220.10 ± 4.12	3.25 ± 0.7	3.5 ± 0.6	0.26	12	98.36 ± 4.65

In vitro dissolution study of indomethacin core tablets

The *in vitro* dissolution study of indomethacin core tablets F1, F2, and F3 were done for 1hr in pH 7.4 phosphate buffer as a dissolution medium. The results indicated that F1 and F2 formulations lower the amount of drug release, these formulations contain less amount of super disintegrant. Formulation F3 containing higher levels of super disintegrant such as crospovidone showed greater drug release of 97% in 1 hr. Based on the percentage of drug release formulation F3 is selected as the optimized core tablet formulation. The results are shown in Figure 2.

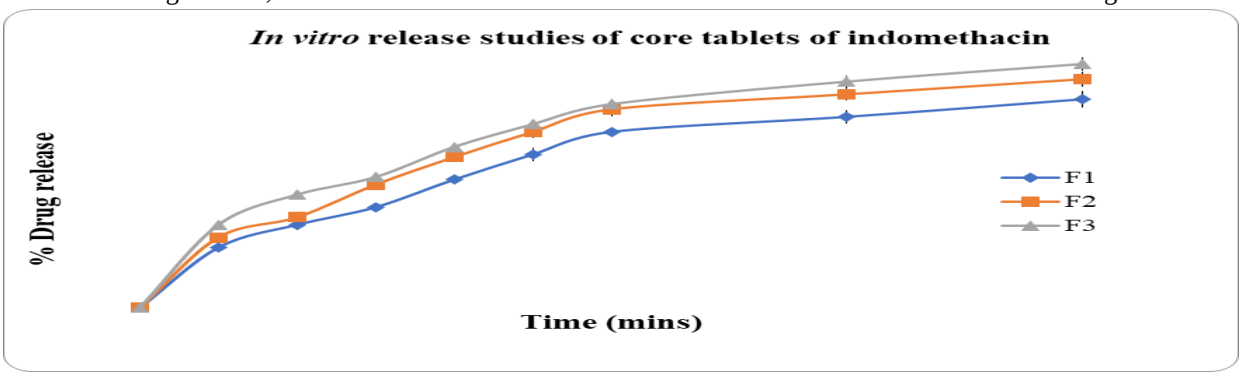

Figure 2. *In vitro* dissolution profile of core tablets in pH 7.4 phosphate buffer

Evaluation of press-coated tablets

Press coated tablets were evaluated for the parameters such as weight variation, thickness, hardness, friability, and core erosion and the results are represented in Table 4.

Table 4: Evaluation of press-coated tablets

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Core erosion (%)
F1	325.6 ± 6.18	5 ± 0.16	5.2 ± 0.27	0.62 ± 0.06	15.6 ± 1.4
F2	342.8 ± 5.29	5 ± 0.19	5.6 ± 0.36	0.73 ± 0.04	21.4 ± 2.9
F3	335.2 ± 8.31	6 ± 0.13	6.4 ± 0.41	0.54 ± 0.07	25.2 ± 1.8
F4	318.4 ± 7.46	5 ± 0.15	5.9 ± 0.29	0.49 ± 0.05	13.8 ± 2.1
F5	348.7 ± 6.38	6 ± 0.17	6.1 ± 0.32	0.27 ± 0.03	3.5 ± 0.46
F6	329.2 ± 8.14	7 ± 0.11	5.8 ± 0.28	0.32 ± 0.08	4.8 ± 0.72

In Vitro dissolution studies of press-coated tablets

The in vitro dissolution studies of indomethacin press-coated tablets were performed by using 7.4 pH phosphate buffer for different formulations, the comparative percentage of drug release studies of press-coated formulations were shown in Figure 3. The % drug release from F1, F2, F3, F4, F4 and F6 were 73.17%, 79.14%, 86.72%, 90.39%, 92.17% and 97.64% respectively.

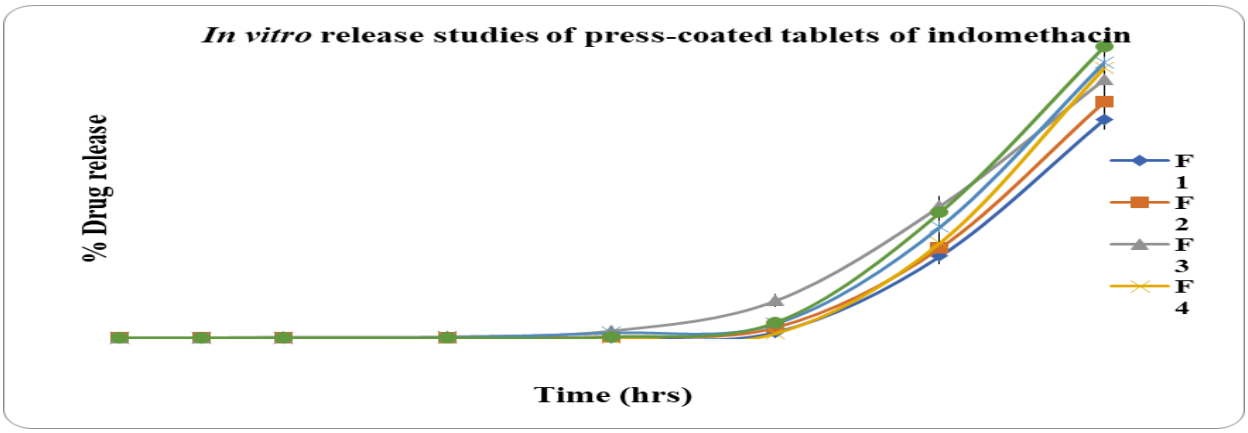

Figure 3: *In vitro* dissolution studies of press-coated tablets of indomethacin

4. CONCLUSION

Finally, it was concluded that the prepared chronotherapeutic drug delivery system of indomethacin can be considered one of the promising formulation techniques for the chronotherapeutic management of rheumatoid arthritis. The lag time depends on the polymer ratio used in the press-coating. The formulation (F3) showed a higher percentage of drug release 97% in 1hr. The press-coated formulation (F6) contains a combination of HPMC K100M and eudragit RL 100 gave a satisfactory release of drug (97.64% in 6 hrs) lag time of 4 hrs and it was found to be successful in achieving pulsatile delivery of the drug. However, there is a further need to determine *in vitro* and *in vivo* correlations.

REFERENCES

[1] Vinay Pandit, Sarasija Suresh, Emerging Role of Biorhythms in Optimizing Treatment of Diseases, *Indian Journal of Novel Drug Delivery*, 2009; 1(1): 2-10.

[2] Neeraj Singh, Nisha, Vivek Gill, Parina Gill, Sukhbir Singh, Chronopharmaceutical drug delivery system-a guided therapy, *International Research Journal of Pharmaceutical and Applied Sciences*, 2013; 3(4): 84-87.

[3] Harshida G Patel, Karishma Patel, UM Upadhyay, Viral H Shah, Chronomodulated drug delivery system: a review, *International journal of pharmacy review and research*, 2013, 3(1): 26-32.

[4] Golla Chandra Mouli, B. Agaiah Goud, J. Subhash, B. Mallikarjun and L. Srikanth. Design and evaluation of press-coated pulsatile delivery of doxofylline tablets. *Acta Scientific Pharmaceutical Sciences*, 2018; 2.11: 58-62.

[5] Shinde PV, Mayee RV, Evaluation of floating press-coated pulsatile release of aceclofenac tablets. A solution for Rheumatoid arthritis, *Asian Journal of Biomedical and Pharmaceutical Sciences*, 2013; 3(17): 16-21.

[6] Mouli GC and Veeresham C. Determination of ursolic acid from solid lipid nanoparticles using high-performance liquid chromatography. *International Journal of Biology, Pharmacy and Allied Sciences*, 2022, 11(3), 1503-1512.

[7] Chandramouli Golla, Subhash Jadav and P.S Raghu. Formulation and characterization of oral disintegrating tablets of valsartan by sublimation and effervescence methods. *Journal of Global Trends in Pharmaceutical Sciences*, 2017; 8(4):4374-4385.

[8] Vure Prasad, Sri Vidya, Madhu Babu& Prakash V Diwan, Formulation of Pulsatile Delivery of Ramipril: A Chrono- Pharmaceutical Approach for the Treatment of Hypertension, *British Biomedical Bulletin*, 2013; 1(1): 005-017.

[9] Dharmarajsinh, Chauhan, Shrenik shah, Formulation and evaluation of pulsatile drug delivery system of aceclofenac for treatment of rheumatoid arthritis, *International Journal of Pharm and Pharmaceutical Sciences*, 2012; 4(3): 507-512.

[10] Development of an Optimised Losartan Potassium Press-Coated Tablets for Chronotherapeutic Drug Delivery, *Tropical Journal of Pharmaceutical Research*, 2011; 10 (5): 551-558.