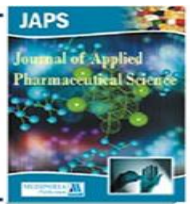
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 09-06-2012
Revised on: 14-06-2012
Accepted on: 20-06-2012
DOI: 10.7324/JAPS.2012.2640

Multiparticulate formulation of Valdecoxib for the treatment of rheumatoid arthritis

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ABSTRACT

An oral controlled onset dosage form intended to approximate the chronobiology of rheumatoid arthritis was proposed for colonic targeting. The multiparticulate system comprising of non-pareil seeds coated with Eudragit S100 was designed for chronotherapeutic delivery of valdecoxib. The drug was coated onto non-pareil seeds by powder layering technique using the conventional coating pan. Different coat weights of non-aqueous dispersions were applied onto the drug-coated pellets using spray coating technique. In vitro dissolution tests of the coated pellets were performed in different pH media for a period of 11 hours. The in-vitro dissolution tests showed that the release of valdecoxib from the coated pellets depended on the pH of the dissolution fluid and the coat weights applied. All the formulations exhibited no release of drug in the pH 1.2 and pH 4 buffers; drug release took place in phosphate buffer of pH 7.4. Further intactness of the drug in the formulation and the uniformity of the polymer coating were checked by the infrared study and scanning electron microscopy. Stability studies inferred that the drug undergoes no considerable degradation pattern at room temperature and 40^{o}C even after three weeks. All the above results show that the formulation could be highly advantageous in the chronotherapy of rheumatoid arthritis with appreciable drug release and physiochemical properties.

Keywords: Oral controlled onset dosage form, Chronobiology, Eudragit S100, Valdecoxib, Powder layering technique, multiparticulate system.

INTRODUCTION

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness (Isadora S et.al, 1997). A chronobiological pattern has been observed with arthritis pain (William J et.al, 2001) People with rheumatoid arthritis, the pain usually peak in the morning and decreases as the day wears on, it is due to etiopathogenesis of rheumatoid arthritis (Harsh M, 1998). For rheumatoid arthritis sufferers, the optimal time for anti-inflammatory drug such as ibuprofen would be more effective when taken after the evening meal.

The standard treatment for RA includes non-steroidal anti-inflammatory drugs such as selective, non-selective NSAIDS and corticosteroids. NSAIDS are associated with extensive side effects, the most prevalent being gastrointestinal (GI) disturbances.

Recently most of the newly developed anti rheumatoid arthritis agents have been once – daily, long acting preparations such as acetyl salicylic acid, diclofenac SR, naproxen EC (Neal MD et.al, 1999). However the drawbacks associated with the conventional therapy includes, the absorption kinetics of conventional dosage forms is not adequate in a morning when the need of patient is greatest and drug levels of once-a-day formulations that have night time dosing indication tend to fall off towards end of the 24 hour dosing interval resulting in reduced protection against the pain when the need is more.

The aim of the research project is to design and develop an oral site specific controlled onset and extended release delivery system of valdecoxib to modulate the drug level with respect to the circadian rhythm of rheumatoid arthritis pain. In this project, we have attempted to develop a novel dosage form by using a chronotherapeutic approach. Bed time administration of the dosage form will parallel the circadian rhythm of rheumatoid arthritis pain and provide maximum protection in the initial hour of the morning till late afternoon.

A new multi particulate dosage form consisting of a hydrophobic core, which is further coated with a pH dependent swelling polymer (acrylic polymer such as Eudragit S100) is proposed for colonic specific delivery of drugs (Marta R et al, 1998). With respect to this a pelletization process (Singh G et al, 2012), powder layering process has been adopted (Nastruzzi C et. al, 2000).

EXPERIMENTAL

Materials

Valdecoxib was obtained from Microlabs, (Hosur). Nonpareil seeds (16/24 #) were obtained from Shrushti Pharmaceuticals Pvt. Ltd., Bangalore. All other chemicals and solvents were of suitable analytical grade.

Methods

Preparation of drug loaded nonpareil seeds

Valdecoxib was coated on to 16/24 # non pareil seeds (NPS) by powder layering technique using a traditional coating pan (Marta *et. al*, 1998). Five batches of drug loaded NPS were prepared with different concentrations of binding agent i.e., 0%, 1%, 5%, 10% and 15% (w/w) PVP in alcohol. The percentage of binder used was varied in each batch. The prepared pellets were evaluated for appearance and drug content.

Batch I was prepared by spraying a solution of ethanol over 9 gm of NPS and 1 gm of drug was dusted over it where as Batch II, III, IV and V were prepared by spraying the binder solution, containing specified amount of poly vinyl pyrrolidone in ethanol onto the NPS under specified condition (Table 1) and 1 gm of drug was dusted over the moist NPS and mixed well. Hot air was blown through the mass to dry the drug-loaded pellets. The pellets were then sieved through # 16 and 24-mesh sieve. The pellets retained on # 24 mesh sieve were dried in hot air oven at 45 ^{o}C for 30 min. The drug-coated pellets were evaluated to select the optimum concentration of binder solution. The physical appearance and percentage drug content were the parameters selected for the evaluation.

Table 1: Processing conditions for spray drying.

Processing conditions	Quantity
Batch Size	10 gm
Inlet air temperature	45 – 50^{o}C
Exhaust air temperature	25 - 30^{o} C
Spay rate	5 – 10 ml min^{-1}
Spray nozzle diameter	1mm
Powder dusting rate	5 – 10 gm min^{-1}
Distance: Pellet bed – spray gun	10 – 15 cm
Pan speed (rpm)	20
Pan inclination angle	45^{o}

Evaluation of drug loaded nonpareil seeds

Drug content of drug loaded nonpareil seeds

A known quantity of 100 mg of NPS coated with drug (theoretically containing 10 mg of drug), were dissolved in 100 ml of 0.1N sodium hydroxide. 1ml of the above solution was diluted to 100 ml with 0.1N sodium hydroxide. The solution was filtered using Whatman # 1 filter paper. 5 ml of the filtrate was withdrawn and analyzed at 243 nm taking 0.1 N sodium hydroxide as a blank. % Drug content was calculated according to the formula:

% Drug content = (Actual drug content x 100) /Theoretical drug content.

In- vitro dissolution study

The drug-loaded pellets were subjected to drug in-vitro dissolution study in hydrochloric acid buffer pH 1.2 for 2 hours and phosphate buffer of pH 7.4 thereafter. Dissolution tests were carried out using USP Dissolution Apparatus-I (rotating basket) set at 50 rpm and 37^{o}C. A sample of pellet containing 10mg equivalent of drug was placed in the basket, which was dipped in 900 ml of the dissolution fluid. A sample of 1ml was withdrawn at specified time intervals into a 10 ml volumetric flask. Volume was made up to the mark with appropriate buffer. The absorbance was measured under UV light at 243nm using the appropriate buffer as blank. Dissolution study was performed in triplicate.

Polymer coating on to drug-loaded NPS

Polymer Eudragit S100 was soaked for 3 hours in ethanol containing the specified quantities of talc and PEG 6000. Prior to spraying, the dispersion was homogenized for 15 minutes by stirring at a low rate using a variable speed propeller stirrer. The dispersion was stirred for 30 min before coating as well as throughout the coating process. The composition of the coating solution is shown in table 2. Drug-loaded pellets of 5 gm were charged into the coating pan, the coating dispersion was sprayed on the surface of the pellets under afore mentioned processing conditions until 2%, 4%, 6% and 8% of the theoretical weight gain was achieved. Pellets passing through sieve # 16 and retained on # 22 were used for further studies. Four formulations were prepared with increase in weight gain from 2%, 4%, 6%, 8% which are

termed as formulations I, II, III and IV. The Prepared formulations were further evaluated.

Table. 2: Composition of polymeric dispersion.

Composition	Quantity (gm)
Eudragit S 100	3.25
PEG 6000	0.25
Purified Talc	3.00
Ethanol	q.s

Drug content of polymer coated pellet

A known quantity of 10 mg of the prepared pellets were carefully transferred into a volumetric flask and diluted to 100 ml with 0.1N sodium hydroxide and allowed to equilibrate for a period of 24 hours. Thereafter, the solution was filtered through Whatman # 1 filter paper. 1 ml of the filtrate was diluted to 100ml with 0.1N sodium hydroxide. A sample of 5 ml of the solution was withdrawn and analyzed using Shimadzu UV/Vis spectrophotometer at 243 nm taking 0.1N sodium hydroxide as blank (Shivakumar HN et.al, 2002).

In –vitro release of drug loaded polymer coated NPS

The polymer-coated, drug-loaded pellets were subjected to in-vitro dissolution study in hydrochloric acid buffer of pH 1.2 for 2 hours, acetate buffer of pH 4 for 1 hour and phosphate buffer of pH 7.4 thereafter. Dissolution tests were carried out using USP-I (rotating basket) set at 50 rpm and 37^{o} C. A sample of pellets containing 10 mg of drug was placed in the basket which was dipped in 900ml of the dissolution fluid. A sample of 1ml was withdrawn at specified time intervals into a 10ml volumetric flask. Volume was made up to the mark with appropriate buffer. The absorbance was measured under UV light at 243 nm using the appropriate buffer as blank. Dissolution study was performed in triplicate. The cumulative percentage release vs. time profile for the four formulations batch is shown in figure 2.

Analytical methods

Differential scanning calorimetry (DSC)

The DSC thermo grams were recorded using a differential scanning calorimetry (Q10 TA Instruments, USA). Approximately 2 mg of each sample was placed in an aluminium pan and heated from 30 to 300^{o} C at a scanning rate of 10^{o} C/min under a stream of nitrogen.

Fourier Infrared spectroscopy

The selected formulation was subjected to FTIR analysis in order to confirm the intactness of drug in formulation along with drug and excipients. The spectra obtained was compared using Shimadzu FTIR 8400, spectrophotometer.

Particle size analysis:

The particle size of the formulation was determined by a conventional method using an optical microscope (Pandit V *et al.,* 2012). The eye piece was calibrated using a stage micrometer. The sample was mounted on the slide using glycerin base and particle size was measured (Martin A et.al).

Scanning electron microscopy

Morphology of the selected formulation was checked by scanning electron microscopy. Cleaned brass specimen studs were used for mounting the samples. Wet solvent paint was applied on the studs and while the paint was wet, the pellets were placed on each stud and allowed to dry. Then the sample was observed in the Joel JSM 840A scanning electron microscope. The scan obtained is shown as photograph.

Stability studies

The selected formulation was stored at room temperature and 40^{o}C for a period of three months. Physical stability was analyzed by appearance and chemical stability was carried out by estimating the percentage drug content (Singh G et al 2012). The samples were withdrawn at weekly interval and the drug content was analyzed spectrophotometrically at 243nm.

Table 3: Composition of selected formulation.

Composition	Quantity used (gm)
Drug	0.5
NPS	4.5
PVP (% w/w)	10.0
PEG 6000 (% w/w)	0.250
Talc (% w/w)	3.0
Eudragit S100 (% w/w)	3.25
Ethanol	q.s

RESULTS AND DISCUSSION

An oral, controlled-onset extended release chronotherapeutic drug delivery system of valdecoxib was designed and various studies were carried out. The results obtained after the study has been discussed here.

Determination of optimal binder concentration

The powder layering technique produced drug-loaded NPS of good quality, i.e. having good drug content as well as appearance, was simple, easy and economical means of coating drug on to NPS. The optimal percentage of binder to be used was studied by varying the binder content in the formulation. PVP in 10% w/w concentration produced optimal binding ability. As the concentration of PVP increased, the drug-coated NPS became sticky and formed aggregates. In concentration below 10%, the drug coated NPS showed good appearance but poor drug content. When no PVP was used, the NPS showed poorest drug content due to flaking which is shown in table 4.

In vitro drug release of the drug coated NPS using an optimum binder concentration

In vitro studies indicated that in pH 7.4 buffer 98.2 % of drug release takes place within 3.5 hrs. The in vitro drug release data for drug coated NPS with 10 % w/v PVP is shown in table 4 and the cumulative percentage release vs. time profile is shown in figure1.

Table 4: Effect of varying concentrations of PVP on drug coated NPS.

Batch	PVP(%w/w)	Appearance	Absorbance	Actual Drug Content	Theoretical Drug Content	% Drug Content
I	0.0	Flaky	0.022	4.615	10	46.15
II	1.0	Flaky	0.029	6.083	10	60.83
III	5.0	Good	0.038	7.972	10	79.72
IV	10.0	Good	0.044	9.230	10	92.30
V	15.0	Aggregates	0.046	9.650	10	96.50

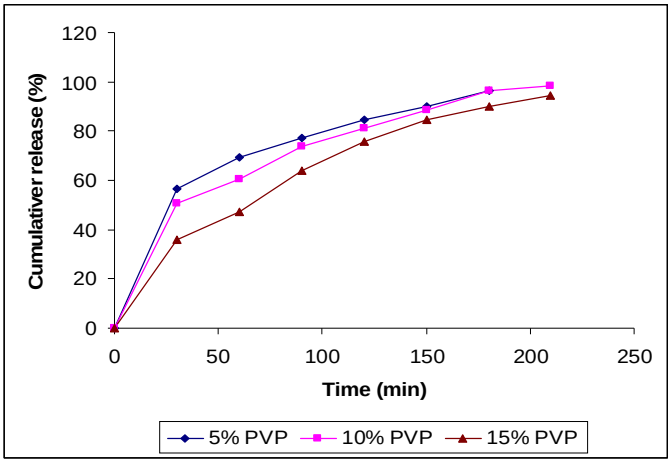

Fig. 1: Comparative drug release profile of valdecoxib-coated NPS using 5%, 10% and 15% w/w PVP.

Studying the effect of polymer on drug release rate

The drug-loaded NPS were coated with polymer Eudragit S100 and were subjected to drug content and *in-vitro* dissolution studies. From the results drug content and the *in-vitro* drug release profile, it was observed that Eudragit S100 (with practical weight gain up to 6%) coated on to pellets had 96.86% of drug content and retards the drug release for as long as 7 hours respectively (Figure 1). Eudragit S100, being an enteric polymer that dissolves above pH 7.0, was coated onto the drug coated pellets to provide enteric coating for colon targeting.

Drug content of polymer coated drug coated NPS

All the investigated formulations consisting of polymer coated drug coated NPS was found to have an acceptable drug content, which is given in table 5.

Table. 5: Effect of varying concentration of Eudragit S100 on drug coated NPS.

Formulation	Eudragit S100 (%w/v)	Actual drug content	Theoretical drug content	% Drug content
I	2	6.923	10	69.23
II	4	7.972	10	79.72
III	6	9.650	10	96.86
IV	8	9.230	10	92.3

Table 6: Particle size distribution of selected formulation.

Particle size range (µm)	Mid point (d)	Frequency (n)	nd	Average particle size (µm)
400-500	450	1	450	653
500-600	550	23	12650	
600-700	650	57	37050	
700-800	750	10	7500	
800-900	850	9	7650	
900-1000	950	-	-	
		∑n = 100	∑nd = 65300	

In-vitro drug release

The *in-vitro* studies indicated that at pH 1.2 and 4.0 there was no drug release from the formulation. This clearly suggested that the formulation was well protected by a polymer coat, thereby not allowing any leakage of drug to occur in the acidic medium. This was attributed to the enteric coating of polymer Eudragit S100 which dissolves only above pH 7.0. Further *in-vitro* studies were carried out using phosphate buffer pH 7.4 where in the drug release was studied for 8 hours. The *in-vitro* drug release data for 4 formulations clearly suggest that on increasing the percentage of S100, there is an increase in the time duration for the maximum release of the drug to take place, thereby the system acts as an efficient barrier in retarding the release of the drug (Figure 2).

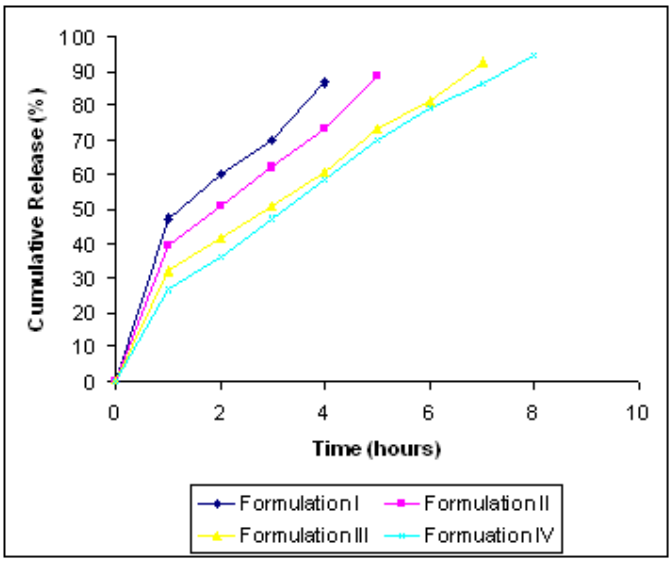

Fig. 2: Comparative drug release profile of Formulation I, II, III and IV in phosphate buffer pH 7.4.

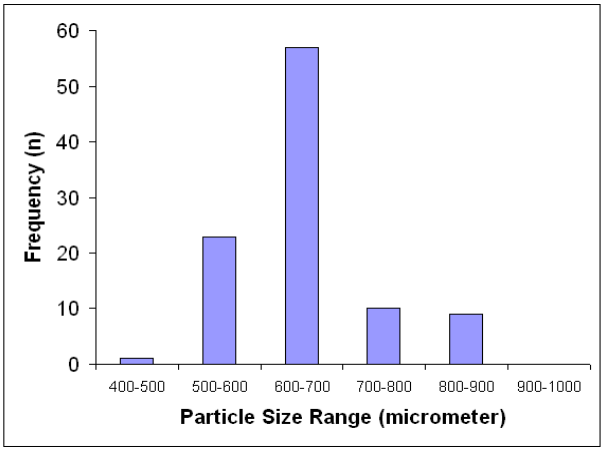

Fig 3: Particle size distribution of selected formulation.

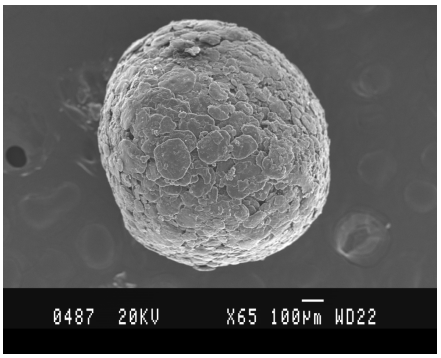

Fig. 4: SEM of drug coated NPS.

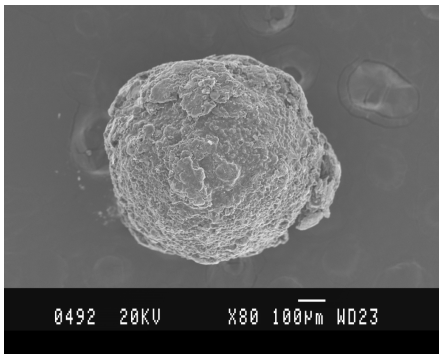

Fig. 5: SEM of polymer coated NPS.

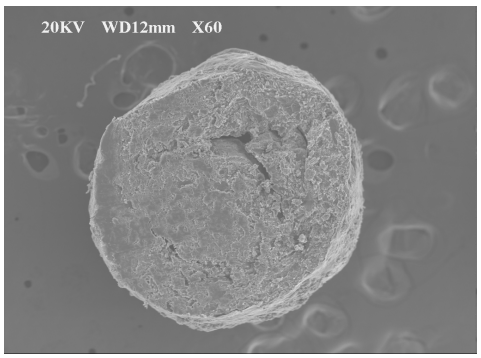

Fig. 6: SEM of transverse section of polymer coated NPS.

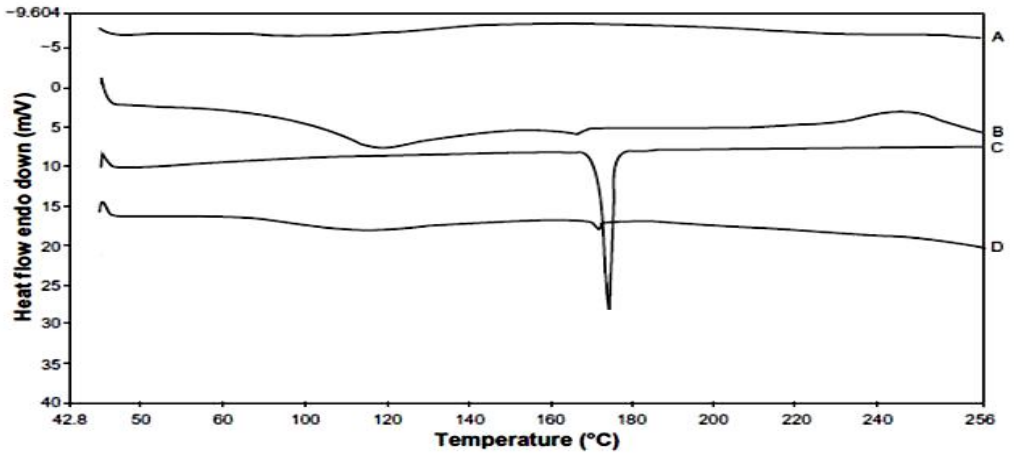

Fig. 7: DSC thermograms of Eudragit S100 (**A**) PVPK30 (**B**) valdecoxib(**C**) and physical mixture of valdecoxib, PVPK30 and Eudragit S100 (**D**)

Differential scanning calorimetry

The interaction between valdecoxib and Eudragit S 100 is studied by performing DSC studies on the individual components. Thermal behavior of pure drug and corresponding drug carrier system are depicted in Figure. The DSC curve of valdecoxib exhibited a sharp endothermic peak (Tpeak = 173.8°C) corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity (Figure 7). This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer or it could also be due to dilution effect of the amorphous polymer. DSC patterns suggest that the process of preparing drug loaded polymer coated multiparticulates could not induce any interaction at the molecular level.

Infrared spectroscopy

Integrity of the formulation was checked by taking IR spectra of the selected formulation using Shimadzu FTIR 8400 spectrometer. FTIR spectrum of the pure valdecoxib showed characteristic peaks at 3377 cm−1 and 3250 cm−1 due to N-H stretching of sulfonamide and at 1334 cm−1 and 1150 cm−1 due to S=O stretching vibrations of sulfonamide.

The spectrum of Eudragit S100-coated multipaticulates of valdecoxib containing polyvinyl pyrrolidone showed peaks at 3377 cm−1 and 3250 cm−1 due to valdecoxib, at 1728 cm−1 due to Eudragit S100, at 1620 cm−1 due to PVP, and at 1334 cm−1 and 1155 cm−1 due to valdecoxib and Eudragit S100. Therefore the spectra's obtained suggested that there was no interaction occurred in between the drug and the excipients.

Particle size analysis

Particle size data of both the polymer coated and uncoated pellets clearly indicated the increase in particle size from 636 µm to 653 µm as the drug loaded NPS was coated with Eudragit S100.

Scanning electron microscopy

The transverse section of the prepared pellets, the thickness of the polymer coat can be seen. The polymer film appears to be continuous and uniform (Figure 4-6).

Stability study

The selected formulation showed no considerable degradation pattern on carrying out stability study for a period of three weeks. The study showed no considerable degradation pattern of drug at room temperature and 40^{o}C.

CONCLUSION

The aim of this project was to optimize the therapy of rheumatoid arthritis by applying a chronotherapeutic approach. An oral, controlled onset extended release formulation of valdecoxib, intended to approximate the chronobiology of rheumatoid pain and proposed for colonic targeting was successfully developed. The formulation dosed at 10 p.m., will release the drug in the distal ileum (pH >7.0) after a lag-period of about 5 hours. Peak levels will be obtained at about 4 a.m. and will be maintained for 11 hours. Hence, the most significant reduction in rheumatic pain will be achieved in between 4 a.m. and 4 p.m. Rheumatic pain is at its peak between 6 a.m. and 8 a.m. therefore the drug is widely available in the system at the time of need. Hence, the formulation could be highly advantageous in the chronotherapy of rheumatoid arthritis with appreciable drug release and physiochemical properties.

REFERENCE

Harsh M. Textbook of Pathology, 3rd Edn., Jaypee Brothers, Medical Publishers. Delhi (1998) 1006-08.

Isadora S. A Time to Heal: Chronotherapy Tunes In to Body's Rhythms. FDA Consumer Magazine. 1997; 3-9.

Jindal KC., Chaudhary RS., Khanna S. Enteric film coating. The Eastern Phamacist, 1994; XXXVI: 433: 41-47.

Manavalan R., Ramaswamy C. Physical Pharmacy. 2nd Edn. Vighnesh Publishers. Chennai (2001) 284-95.

Marta R, Jose LVJ, Dolores T. Design of new multiparticulate system for potential site-specific and controlled drug delivery to the colonic region. J Controlled Release. 1998; 55: 1: 67-77.

Martin A. Physical Pharmacy. 4th Edn. B.I. Waverly Pvt. Ltd. New Delhi 1999; 430-36.

Michael H., Gaston L. Chronotherapeutics. Pharm News. 1997; 4; 2-6.

Nastruzzi C., Cortesio R., Esposito E., Genovesi A., Spadoni A., Vecchio C. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS Pharm Sci Tech. 2000; 1: 2-10.

Neal MD. Sustained Release Enteric Coated NSAIDS: Are they Really GI Safe. J Pharm Sci. 1999; 2:1:5-14.

Pandit V, Pai RS, Yadav V, Devi K, Surekha BB, Inamdar MN. Pharmacokinetic and pharmacodynamic evaluation of floating microspheres of metformin hydrochloride. Drug Dev Ind Pharm 2012;1-

Reinberg A., Levi F., Clinical chronopharmacology with reference to NSAID's. Scand J. Rheumatol. Suppl. 1987; 65:118-22.

Sanders SW., Moore JG. Gastrointestinal Chronopharmacology: Physiology, Pharmacology a therapeutic implications. Pharmacol Ther. 1992; 54: 1-15.

Shivakumar HN., Suresh S., Venkatram S. Design and evaluation of a multiparticulate system for chronotherapeutic delivery of diclofenac sodium. Ind J Pharm Sci. 2002; 64:2:133-37.

Singh G, Pai RS, Devi VK. Response surface methodology and process optimization of sustained release pellets using Taguchi orthogonal array design and central composite design. J Adv Pharm Technol Res 2012;3:30-40.

Singh G, Pai RS, Pandit V. Development and validation of a HPLC method for the determination of trans-resveratrol in spiked human plasma. J Adv Pharm Tech Res 2012;3:130-5.

Willard HH, Meritt LL, Dean JA, Settle FA. Instrumental Methods of Analysis. 6th Edn. CBS Publishers and Distributors. Delhi (1986) 177-216.

William JE. Timing treatment of disease. Postgraduate Medicine 2001; 110:2-8.