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DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF PIROXICAM AND SULFASALAZINE

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Abstract
The objective of the present study is to formulate and evaluate an oral pulsatile drug delivery of piroxicam and sulfasalazine, based on chronopharmaceutical approach for the treatment of Rheumatoid arthritis and Osteoarthritis. Time controlled release of drug from tablets designed to release drug after a predictable lag time, intended for oral chronotherapy. The basic design consists of a core tablets of piroxicam and sulfasalazine were prepared by direct compression method. The tablets were coated with different polymer ratios to the different formulations. The prepared pulsatile tablets were evaluated for thickness, hardness, weight variation, drug content and *in-vitro* release profile. On the basis of these evaluation parameters the formulation results of F10 was selected as an optimized formulation for designing the pulsatile device.

Keywords: Pulsatile, Chronotherapeutics, Rheumatoid arthritis, Piroxicam, Sulfasalazine.

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INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R&D sector. Such systems offer temporal/spatial control over the release of drug and grant a new lease of life to a drug molecule for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as "pulsatile release" [1]. The pulsatile effect, i.e., the release of drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time [2]. Such systems are also called time-controlled as the drug released is independent of the environment. Pulsatile drug delivery systems are gaining a lot of interest and attention these days. However, the major bottleneck in the development of drug delivery systems that match circadian rhythms (chronopharmaceutical drug delivery system: ChrDDS) may be the availability of appropriate technology [3]. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases. Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness. A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutical system.

Advantages of pulsatile drug delivery system

There are many advantages of pulsatile dosage form over conventional dosage form [4]

- Increases absorption and bio-availability of the drug than the conventional immediate release or sustained release dosage forms due to its ability to release drug in burst manner at target site.
- Reduces dose of drug without affecting the therapeutic benefits.
- Decreases side effect.
- Improved compliance.

- Chronotherapy, programmed delayed release provides optimal treatment for diseases.
- Pulse release allows multiple dosing in a single dosage form.
- Allows site specific release for local treatment of diseases.

MATERIALS AND METHODS

Materials

Piroxicam a generous gift from Euro labs, Hyderabad, sulfasalazine from Aurobindo pharmaceutical labs, Hyderabad, Micro crystalline cellulose from Active pharmaceutical labs, Hyderabad, Lactose from Zydus cadila, Ahmadabad, sodium starch glycolate and magnesium stearate were from S.D fine chemicals, Mumbai, HPMC from Signet chemicals corporation, Mumbai, Eudragit from Micro labs, Bangalore, Ethyl cellulose from oxford laboratories, Mumbai, methanol from Merck pvt ltd.

Pre compression evaluation

Micrometric properties

Flow ability of the pre compression mixture of core tablets was performed by measuring the angle of repose by fixed funnel method. A measured amount of the powder was allowed to flow through the funnel fixed at a constant height (h=2.5 cm) and mean diameter (2r) of the powder pile was measured. The bulk density (BD) and tapped bulk density (TBD) of pre compression mixture was determined using bulk density apparatus (Electro Lab, India). Carr's index and Hausner's ratio were calculated using BD and TBD values [5].

Methodology

Formulation of rapid release core tablets by direct compression

The inner core tablets were prepared by using direct compression method as per formulation variable shown in *Table 1*. Powder mixture of piroxicam, sulfasalazine, micro crystalline cellulose, sodium starch glycolate, lactose monohydrate ingredients were dry blended for 20 min followed by addition of magnesium stearate. The mixtures were then further blended for 10 min. The resultant powder blend was manually compressed using hydraulic press at a pressure of 1 ton with 9mm punch and die to obtain the core tablet [6].

Formulation of mixed blend for coating layer

The various formulation compositions containing HPMC, Ethyl cellulose and Eudragit as shown in Table 2 were weighed separately dry blended at about 10 min and to these blend Dibutyl

phthalate, ethyl alcohol and dichloromethane were added to prepare coating solution. And these solutions were used as press coating material to prepare press coated pulsatile tablets.

Preparation of coated tablets

The Optimized core tablets were coated with different coating compositions were evaluated for providing pulsatile drug delivery of Piroxicam and Sulfasalazine. Initially Tablets were coated with Ethyl cellulose polymer Coating solution – I to first four formulations in order to retard the drug release from the compressed tablets. From formulations F5 to F8 coated with HPMC coating solution – II, to retard the drug release. The formulations F9 & F12 were coated with Eudragit polymer and F10 & F11 were coated with coating solution – III, which contain HPMC and Eudragit gives zero release in acidic media for first two hours:

Table 1: Different formulations of piroxicam and sulfasalazine tablets.

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Piroxicam	10	10	10	10	10	10	10	10	10	10	10	10
sulfasalazine	500	500	500	500	500	500	500	500	500	500	500	500
Micro crystalline cellulose	100	100	100	100	100	100	-	-	-	-	-	-
Ethyl cellulose	78	68	58	48	-	-	-	-	-	-	20	-
HPMC	-	-	-	-	38	28	78	68	-	20	-	-
Eudragit	-	-	-	-	-	-	-	-	58	28	18	28
Lactose	-	-	-	-	-	-	100	100	100	100	100	100
Sodium Starch Glycolate	10	20	30	40	50	60	10	20	30	40	50	60
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total wt	700	700	700	700	700	700	700	700	700	700	700	700

Table 2: Coating solution I

Ethyl cellulose	6%
Dibutyl phthalate	0.16%
Ethyl alcohol (200 proof)	10ml
Dichloromethane	10ml

Table 3: Coating solution II

HPMC	8.5%
Dibutyl phthalate	0.1%
Ethyl alcohol	10ml
dichloromethane	10ml

Coating solution (I) is used for (F1,F2,F3,F4) Coating solution (II) for (F5,F6,F7,F8)

Table 4: Coating solution III

HPMC	7.8%
Eudragit	2.2%
Dibutyl phthalate	0.1%
Ethyl alcohol	10ml
Dichloromethane	10ml

Coating solution (III) is used for formulations (F9, F10, F11, F12)

Physicochemical parameters of core tablets and coated tablets

The tablets were checked for weight variation, wetting time. Tablet thickness was measured using screw gauge. Hardness of tablets was determined using Monsanto hardness tester, friability was determined using a Roche friabilator (Electrolab, Mumbai) for core tablets and coated tablets individually. Drug content uniformity was determined by dissolving 10mg equivalent amount from the crushed core tablets placed in 100 ml volumetric flask and dissolved in 0.5% SLS solution and 5 ml is taken and diluted with 0.5% SLS solution up to 100 ml. The absorbance of the solution was measured at 334 nm and 354 nm using UV/VIS spectrophotometer (shimadzu corporation) using a reference to a standard calibration curve of the drug. The experiment was performed in triplicate and the average values ± standard deviations (SD) were reported [7].

FT-IR study

The *FT-IR* was performed to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic stretching vibration of conventional formulation. The spectra were recorded over the wave number range of 4000 to 500 cm^{-1} [8].

DSC Study

Thermogram was obtained by using a different scanning calorimeter at a heating rate of 10˚c/min over a temperature range of 50-300 ˚c. The sample was hermetically sealed in an aluminum crucible [9].

***In-Vitro* Dissolution time**

In-vitro dissolution study of core and coated tablets of Piroxicam and Sulfasalazine was carried out using Electro lab TDT-08L USP dissolution test apparatus. The details are given as below:

Electro lab TDT-08L USP dissolution test apparatus

Medium : pH 1.2 buffer solution and pH 6.8 buffer solution;
RPM : 50
Time : 2hrs in pH1.2 followed by dissolution in pH 6.8 buffer solution.

Procedure

Tablet was introduced into the basket of the Electro lab TDT-08L USP dissolution test apparatus and the apparatus was set in motion, 5 ml of sample was withdrawn for 1st half hour at 10 min intervals and after that at 15min intervals and replaced by the respective buffer solutions. Samples withdrawn were analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

Mechanism of drug release

The mechanism of release was determined by fitting the release data into various kinetic equations such as Zero order, First order, Higuchi, and Korsemeyer – Pepas and finding the R^2 values of the release profile corresponding to each model [10].

Stability studies

The stability study of the selected formulations was carried out according to ICH guidelines at 40±2˚c/75±5%RH for 30 days by storing the samples in stability chamber [11].

RESULTS AND DISCUSSION

Compatibility studies by FTIR and DSC analysis

FTIR spectra of piroxicam show a band at 3338.78 cm^{-1} (Figure 3), which indicates that the drug is in the cubic polymorphic form.

Other characteristic bands are attributed to the stretching of different group vibrations: 1629.85 cm^{-1} stretching of amide carbonyl, 1529 cm^{-1} stretching of the second amide band, 1435 cm^{-1} stretching of asymmetric methyl group, 1352 cm^{-1} stretching of symmetric methyl group, 1149 cm^{-1} stretching of –SO2-N- group and 775 cm^{-1} as stretching of *ortho*-disubstitued phenyl.

Pattern of conventional formulation (Figure 3) show band at 3336.88 cm^{-1}which indicates that the piroxicam was remained in the cubic polymorphic form and no interaction with excipients occurred. DSC scan of the piroxicam and sulfasalazine coated tablet and it pure drug are presented in Figure 4 & 5.

The thermograms of piroxicam and sulfasalazine exhibited an endothermic peak at 201˚C and 240˚C corresponding to its melting point range. The thermograms of formulations does not show profound shift in peaks, suggesting that drug has almost same melting point in its formulation. Hence it was concluded that drug had not interacted with the polymer, which indicates compatibility.

Pre-compression parameters

Powder blend used for preparing rapid release core tablets were evaluated for angle of repose, bulk density, tapped density, hausner's ratio, Carr's index and the results shown in *Table* 5. The values for angle of repose, hausner's ratio, Carr's index were found to be in good correlation, indicating that all formulations possess good flow property and compressibility.

Table 5 Micrometric properties of piroxicam and sulfasalazine powder

Formulation code	Angle of repose*	Bulk density* (gm/cm3)	Tapped density* (gm/cm3)	Compressibility Index* (%)	Hausner's ratio*
F1	24.92±0.021	0.372±0.015	0.431±0.075	14.79±0.064	1.16±0.038
F2	22.31±0.026	0.310±0.031	0.392±0.028	13.70±0.064	1.15±0.065
F3	21.25±0.048	0.341±0.011	0.402±0.025	14.86±.0.061	1.17±0.037
F4	19.51±0.022	0.332±0.018	0.403±0.035	13.24±0.036	1.12±0.069
F5	23.92±0.021	0.362±0.015	0.421±0.075	15.79±0.064	1.14±0.038
F6	24.31±0.026	0.340±0.031	0.399±0.028	14.70±0.064	1.17±0.065
F7	26.25±0.048	0.361±0.011	0.412±0.025	13.86±.0.061	1.18±0.037
F8	28.51±0.022	0.342±0.018	0.433±0.035	14.24±0.036	1.15±0.069
F9	24.91±0.035	0.335±0.012	0.422±0.038	15.40±.0.095	1.14±0.099
F10	20.92±0.021	0.342±0.015	0.411±0.075	15.79±0.064	1.15±0.038
F11	28.31±0.026	0.320±0.031	0.399±0.028	16.70±0.064	1.16±0.065
F12	27.25±0.048	0.331±0.011	0.406±0.025	15.86±.0.061	1.18±0.037

Post compression studies

Table 6: Evaluation of physical parameters of compressed tablets of piroxicam and sulfasalazine

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content	Water absorption ratio %
F1	701±1.8	7.20±0.60	8.8±0.151	0.73±1.163	97.96±0.124	82.09±2.30
F2	699±1.3	7.21±0.64	8.6±0.131	0.61±0.263	98.36±0.671	85.25±1.05
F3	698±1.1	7.13±0.73	8.8±0.251	0.63±0.376	98.42±0.682	60.88±0.205
F4	700±1.6	7.12±0.75	8.7±0.108	0.59±0.421	98.60±0.612	78.02±1.37
F5	702±1.8	7.19±0.98	7.2±0.648	0.54±0.594	96.90±0.630	69.08±3.85
F6	701±1.8	7.27±0.60	9.8±0.151	0.73±1.163	98.96±0.124	85.09±2.30
F7	697±1.3	7.21±0.64	9.6±0.131	0.61±0.263	95.36±0.671	86.25±1.05
F8	698±1.1	7.14±0.73	7.8±0.251	0.63±0.376	97.42±0.682	79.80±0.205
F9	705±1.6	7.14±0.75	8.7±0.108	0.59±0.421	96.70±0.612	79.02±1.37
F10	706±1.8	7.20±0.98	6.2±0.648	0.54±0.594	99.60±0.630	69.08±3.85
F11	702±1.8	7.19±0.98	7.2±0.648	0.54±0.594	96.90±0.630	69.08±3.85
F12	701±1.8	7.27±0.60	9.8±0.151	0.73±1.163	98.96±0.124	85.09±2.30

Table 7: Cumulative % drug release of core piroxicam and sulfasalazine tablets of different formulations (F1 to F12)

S.No	Time (min)	Cumulative % of drug release from Piroxicam and sulfasalazine											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	5	13.2	14.6	15.4	18.9	19.5	17.8	19.4	14.9	18.9	19.9	20.9	21.9
2	10	25.6	28.6	29.6	24.6	29.6	27.6	32.6	25.6	35.6	33.6	35.6	39.6
3	15	41.2	31.2	45.2	45.2	41.2	47.2	41.2	47.2	46.2	45.2	46.2	45.2
4	20	53.8	55.8	58.8	59.8	57.8	54.8	57.8	56.8	57.8	59.8	65.8	59.8
5	25	61.8	62.8	63.8	64.8	62.8	64.8	63.8	64.8	64.8	64.8	66.8	67.8
6	30	71.2	61.2	69.2	71.4	71.6	69.3	69.5	69.8	69.7	71.7	66.9	71.0
7	40	75.5	74.4	73.2	79.9	78.9	79.8	78.5	76.5	79.8	85.5	75.9	79.9
8	50	84.4	85.2	89.1	91.1	87.7	82.2	84.4	87.7	82.2	99.8	85.5	91.5

Fig. 1: In-vitro Drug release of all core formulations

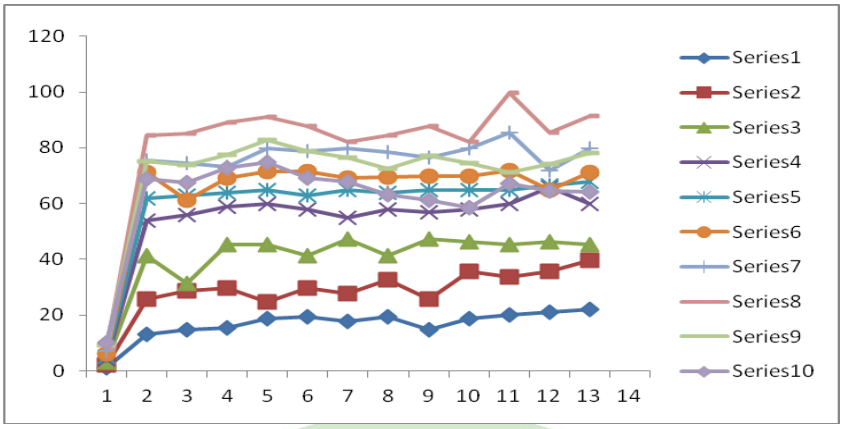
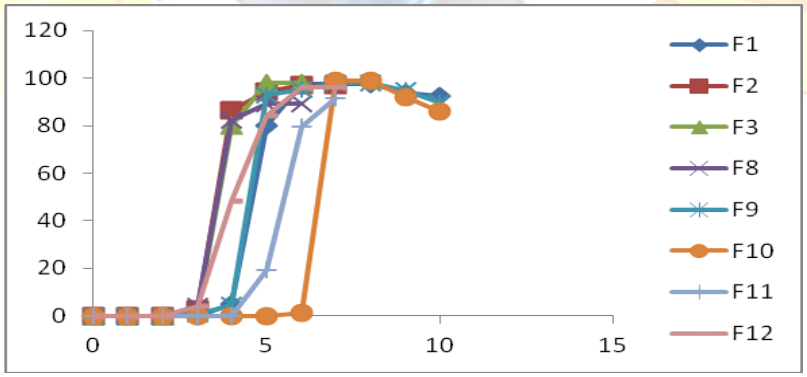


Table 8: Cumulative percent drug release of coated piroxicam and sulfasalazine tablets of different formulations (F1 to F12)

Time (Hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
pH 1.2												
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
pH 6.8												
3	1.87	2.46	2.7	1.61	3.12	1.54	2.18	3.91	4.64	2.46	1.97	1.34
4	15.8	18.09	14.2	20.74	17.82	16.31	17.55	18.48	24.12	14.67	16.10	15.01
5	26.1	34.09	25.88	51.14	29.41	33.24	32.51	35.85	46.31	25.62	34.12	38.08
6	37.2	71.64	77.81	82.61	66.74	57.19	74.53	84.01	71.67	64.38	56.74	72.19
7	49.8	83.12	81.27	99.06	86.19	82.76	86.69	92.12	98.06	98.86	91.03	94.51
8	66.9	97.31	95.45	99.06	98.01	96.20	94.24	93.54	98.09	99.96	91.41	98.1
9	79.8	--	--	--	--	--	--	--	--	--	--	--
10	92.2	--	--	--	--	--	--	--	--	--	--	--

Fig 2: Cumulative % drug release of all coated formulation



Characteristics of rapid release core and coated tablets

The rapid release core and coated tablets were tested for diameter, thickness, hardness, friability, drug content uniformity and results are presented in table VII. Diameter, thickness, and hardness were found to be within acceptable limit. The friability was <1% indicating good mechanical resistance of the tablet.

Fig 3: FTIR spectrum of Pure Piroxicam

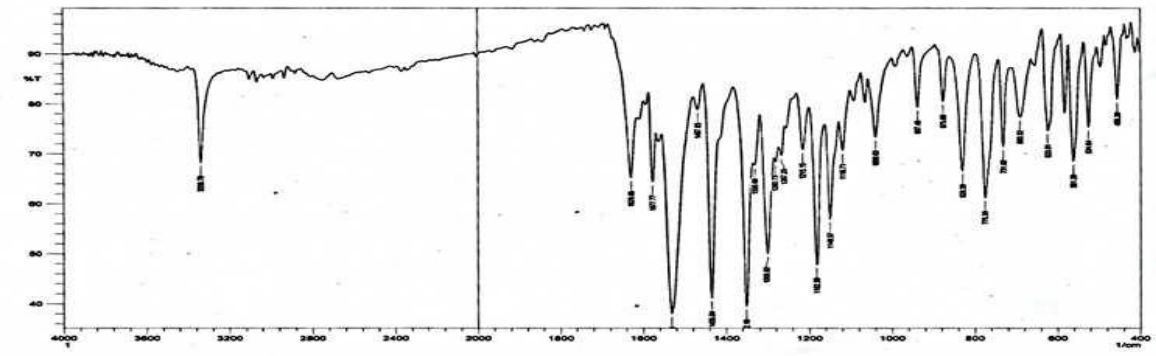


Fig 4: FTIR Spectrum of Sulfasalazine (SSZ)

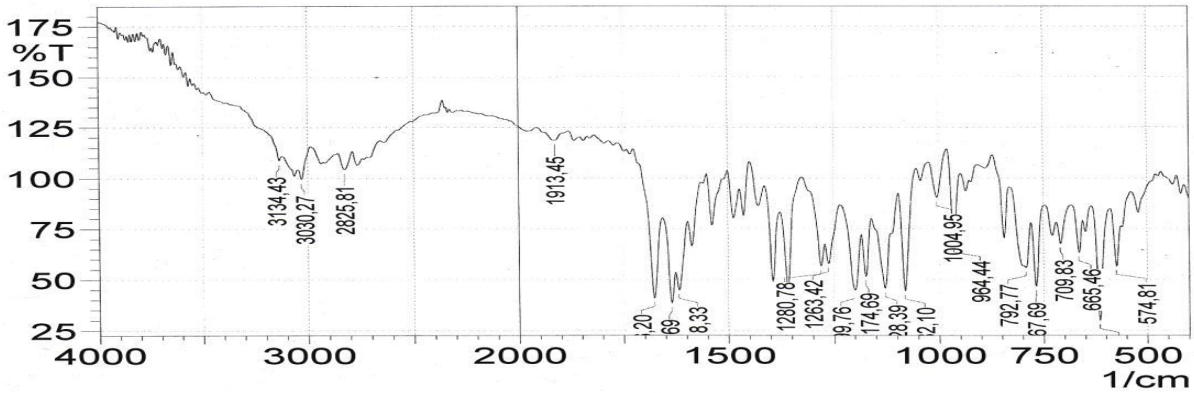


Fig 5: FT-IR spectrum of optimized formulation (F10)

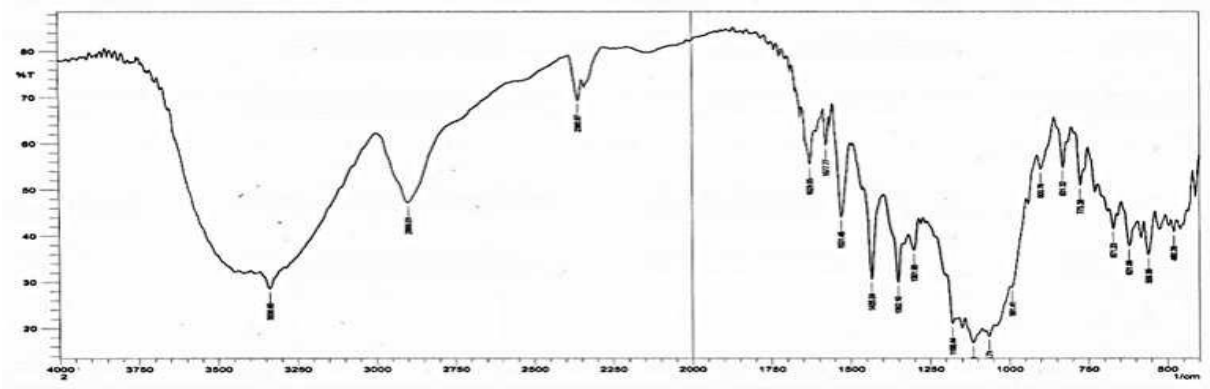


Fig. 6: DSC Thermo graph of sulfasalazine

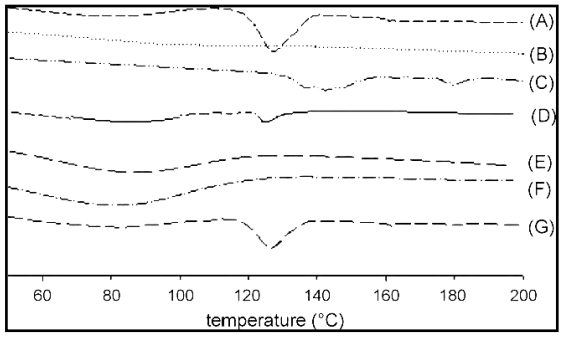
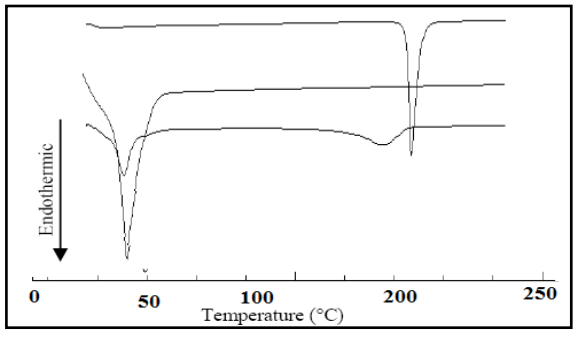


Fig.7: DSC Thermo graph of piroxicam



CONCLUSION

The aim of this study was to explore the feasibility of time and time dependent colon specific, pulsatile drug delivery system of Piroxicam and Sulfasalazine to treat the rheumatoid arthritis. A satisfactory attempt was made to develop Pulsatile tablets by using time dependent polymers (Eudragit L/S100, HPMC, Ethyl cellulose) and further the time dependent, pulsatile tablets was designed and evaluated. The data obtained from the study of "Development and evaluation of pulsatile drug delivery system of Piroxicam and Sulfasalazine" reveals following conclusion:

- Eudragit L-100 and S-100 (in the ratio 1:2), HPMC, Ethyl cellulose are suitable for preparation of tablets for colonic targeting.
- The flow properties of all the drug powder were good as indicated by low angle of repose ($\theta < 40^{o}$).The good flow properties suggested that the microspheres produced were non-aggregated.
- The entrapment efficiency was good in all the cases. This suggested that optimized parameters were used in the method of preparations.
- *In-vitro* drug release of Pulsatile Tablets showed biphasic release pattern for all tablets with initial burst release effect, which may be attributed to the drug loaded onto the surface of the particles.
- On the basis of, particle size, drug content, Scanning Electron Microscopy, IR-study, *in-vitro* release studies and its kinetic data, FM-10 was selected as an optimized formulation for designing pulsatile Tablets.
- From all obtained results, it was found that the order of sustaining capacity of polymer is HPMC > Eudragit > Ethyl cellulose.
- Hence, finally it was concluded that the prepared pulsatile drug delivery system can be considered as one of the promising formulation technique for preparing colon specific drug delivery systems and hence in chronotherapeutic management of arthritis.

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