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Formulation And *In Vitro* Evaluation Of Indomethacin Pulsincap For Colon Targeting

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ABSTRACT

Rheumatoid arthritis (RA) is traditionally considered as a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. The symptoms of rheumatoid arthritis are severe in early morning hours, so an attempt has been made to overcome the problem by delaying drug release by colon targeting to maintain peak plasma concentrations in early morning hours[1]. Indomethacin, a non-steroidal anti-inflammatory drug effectively used for treatment of inflammation and pain caused by rheumatoid arthritis, was selected as a model drug[2]. Indomethacin has a plasma half life of 4.5hr. Its administration rate is frequent due to its short half life. The aim of this study was to develop a pulsincap containing micro encapsulated Indomethacin (microsponges) to relieve pain and inflammation caused by rheumatoid arthritis in early morning hours which are targeted to colon and also to reduce the gastric irritation.

KEYWORDS

Pulsincap;
Colon target;
Pulsatile drug delivery;
Arthritis;
Micro sponge;
Indomethacin.

INTRODUCTION

"Arthritis" literally means "inflamed joints. Osteoarthritis is also called degenerative joint disease; it is the most common type of arthritis. It is associated with a breakdown of cartilage in joints and can occur in almost any joint in the body. It most commonly occurs in the weight bearing joints of the hips, knees, and spine. It can also affect the fingers, neck, and large toe. Osteoarthritis causes the cartilage in a joint to become stiff and lose its elasticity, making it more susceptible to damage. Over time, the cartilage may wear away in some areas greatly decreasing its ability to act as a shock absorber. As the cartilage deteriorates, tendons and ligaments stretch, causing pain. Generally the small intestine is considered as the primary site for drug absorption and therefore the preferred part of the gastrointestinal tract for

targeting with various controlled release technologies. Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity, and a much greater responsiveness to absorption enhancers. The various categories of drugs being targeted to their site of action include drugs which are unstable/unabsorbed in the upper GIT and drugs which are required for treatment of local colonic pathologies. Additionally, this site may be useful for delivery of those drugs where a delay in drug release is required from a therapeutic point of view.

Pulsatile drug delivery systems

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action and at the right time thus providing spatial and temporal delivery and increasing patient compliance[3]. These systems are designed according to the circadian rhythm of the body[4]. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. Patients suffering from osteoarthritis are reported to have less pain in the morning than night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours. 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 fallow the lag time. Such systems are also called time controlled as the drug released is independent of the environment. These systems beneficial for drugs having high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT,targeting to colon. And cases where night time dosing is required. Pulsatile drug delivery systems is a single-unit systems that are mostly developed in a capsule form. A general architecture of such systems consists of an insoluble capsule body[5] housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The Pulsincap system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. The lag time can be controlled by manipulating the dimension and the position of the plug. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers(e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer(e.g., pectin). These formulations were well tolerated in animals and healthy volunteers; however, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher ph region of small intestine.

Indomethacin[6] which is a non-steroidal anti inflammatory agent with anti pyretic and analgesic properties is also effective in the management of patients with moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder, and acute gouty arthritis. But it has contrain dications sich as active peptic ulcer, recurrent indigestion(relative contraindication), care should be taken in patients with difficult to control hypertension or heart failure, care should be taken in patients on anticoagulants, suppositories not be used in patients with rectal bleeding or proctitis.

Pregnancy, thus microencapsulated[7] indomethacin was formulated to pulsin cap drug delivery and evaluated for its pulsatile dru release using sitable buffers. Their physicochemical properties were also been studied.

EXPERIMENTAL

Formulation and characterization of indomethacin microsponges includes preparation of indomethacin microsponges with ethyl cellulose(46cps) polymer, Characterization of the prepared microspongesand *In vitro* dissolution profile of prepared microsponges and development of pulsincap dosage forms includes Coating the body of the capsule shell, Preparation and

coating of hydrogel plug, formulation of pulsincap dosage forms, determination of physicochemical parameters of the dosage forms, *in vitro* dissolution profile of pulsincap dosage forms, kinetic analysis of dissolution data. The drug indomethacin were gifted by Kniss laboratories, Chennai. The polymers used were gifted by hetero drugs. The reagent used were of analytical grade.

According to pharmacopeal specifications buffer solution such potassium dihydrogen phosphate solution(0.2M), Sodium hydroxide solution 0.2N), potassium chloridesolution(0.2M), Hydrochloric acid buffer solution(pH 1.2), phosphate buffer pH 6.8solution, phosphate buffer solution pH7.4 has were prepared and used[8].

Preparation of indomethacin microsponges

Indomethacin microsponges were prepared by Quasi-emulsion solvent diffusion method[9]. In this method, the internal phase containing indomethacin and ethyl cellulose was gradually added to distilled water which contained polyvinyl alcohol(PVA) as emulsifying agent. The mixture was stirred using impeller stirrer-remi(model noaa12545) for 2hour to remove the dichloromethane from the reaction flask. The formed microparticles were filtered and washed with distilled water before being dried in oven at 40^0C. For the evaluation of the effect of drug: polymer ratio on the physical characteristics of microsponges, different ratios of drug to ethyl cellulose (1:1,1.5:1,2:1,1:1.5, and 1:2) were tried. In all these formulations the amount of emulsifier, volume of organic solvent and volume of aqueous phase were kept constant. Formula for different batches of indomethacin microsponges were given in TABLE 1.

Practical yield

TABLE 1 : Formula for different batches of indomethacin microsponges

F.no	Indomethacin in (mg)	Ethyl cellulose in(mg)	volume of aqueous phase(ml)	volume of dichloromethane(ml)
F1	500	500	60	20
F2	750	500	60	20
F3	1000	500	60	20
F4	500	750	60	20
F5	500	1000	60	20

Characterization of microsponges[10]

Microsponges were dried at room temperature was then weighed and the yield of microsponge preparation was calculated using the formula:

Practical yield=(The amount of microsponges obtained(g)/Theoretical amount(g))×100

Mean particle size

Determination of mean particle size of indomethacin microsponges with ethyl cellulose was carried out by optical microscopy in which the stage micrometer was employed. A minute quantity of microsponges was spread on a clean glass slide and average sizes of 100 microsponges were determined in each batch.

Scanning electron microscopy (SEM)

The morphology of microparticals was examined with a scanning electron microscope (SEM Jeol JSM-6400, JAPAN) operating at 20kv. The samples were mounted on a metal stub with double adhesive tape and coated with platinum/palladium alloy under vacuum and aanalysed its surface morphology.

Determination of drug content and encapsulation efficiency

Actual amount of Indomethacin present in different sized microsponges was determined by following method. Accurately weighed amount of the dried indomethacin loaded ethyl cellulose micro sponges (100mg) was dissolved in 100ml of chloroform and assayed spectrometrically at 318 nm using double beam (Model Elico-SL -151) Ultraviolet-visible spectrophotometer.

%of drug content=(M_{act}/M_{ms})×100

%of encapsulation efficiency=(M_{act} /M_{the})×100

Where

- M_{act} is the actual indomethacin content in weighed quantity of microsponges.
- M_{ms} is the weighed quantity of powder of microsponges.
- M_{the} is the theoretical amount of Indomethacin in microsponges calculated from the quantity added in the process.

In-vitro dissolution studies

The *in-vitro* dissolution studies of indomethacin microsponges were carried out according to U.S.P.XXIII apparatus 2. (Dissolution apparatus, USP

XXIII, Electro Lab, Model No AA454ub, Mumbai) Microsponges equivalent to 75mg of drug were taken in 900ml of pH 7.4 phosphate buffer maintained at 37^0C. The dissolution media was rotated at 50rpm. At preset time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. Withdrawn samples were filtered and suitably diluted with phosphate buffer pH 7.4 and methanol(1:1). The absorbance of the filtrates was determined at wavelength of 318nm against phosphate buffer of pH 7.4 and methanol(1:1)as the blank. The amount of drug present in the filtrate was then determined from the calibration curve and cumulative percentage of drug release was calculated.

Development of pulsincap dosage forms:

This delivery device uses the basic concept of pH and time dependent drug delivery system. The pulsincap is similar in appearance to the hard gelatin capsule, but the main body is water insoluble. The contents are contained within the body by a hydrogel plug, which is covered by water soluble cap. If necessary the whole unit can be coated with an enteric polymer to avoid the problem of variable gastric emptying affecting dissolution performance. In *in-vivo* once the cap had dissolved, the hydrogel plug begins to swell. When the swelling reaches a critical point, the plug pops out of the capsule body and the contents are released. Depending on the properties of plug used, the time at which this occurs can be controlled

In our study the development of pulsincap dosage form can be divided into following.

- Coating the body surface of the capsule shell.
- Preparation and coating of hydrogel plug.
- Formulation of pulsincap dosage forms.

Coating the body of capsule

As per the design of pulsincap system, the body of capsule shell should be water insoluble. In our work, the hard gelatin capsule shell was coated with water insoluble polymer. Ethyl cellulose[11] was selected among all the available water insoluble polymers for coating.

The body of the hard gelatin capsule was coated with different concentrations (2%, 4%, 6%, and 8%) of ethyl cellulose solutions. The ethyl cellulose solutions were prepared by dissolving the required quantity of ethyl cellulose in acetone. The body of the capsule shell was coated by dipping method and dried completely.

Preparation and coating of hydrogel plug

The hydrogel plug in the pulsincap dosage form should have the property to swell and get ejected in the intestinal fluid. In our study, we have selected gelatin as the hydrogel plug.

In this process 8gm of gelatin powder was taken in a beaker containing 10ml of water and melted. From this, a semisolid mass of appropriate shape, which fits into the body of capsule shell, were prepared with the help of a suitable size mould of different thickness. The prepared gelatin hydrogel plugs were half and full coated with different concentrations (5and10%) of enteric coated polymers namely cellulose acetate phthalate(CAP), hydroxy propyl methyl cellulose phthalate (HPMCP), eudragit L-100[12]. Coating solutions were prepared by dissolving the enteric coated polymers in suitable amount of acetone.

Formulation of pulsincap dosage forms

The selected microsponges equivalent to 75mg of drug were incorporated into the ethyl cellulose coated body of empty capsule shell. Then, it was plugged with formulated hydrogel plug coated with cellulose acetate phthalate (CAP)(P1), hydroxy propyl methyl cellulose phthalate(HPMCP) (P2), eudragit L-100(P3) and there after fixed the normal gelatin capsule cap and the steps involved in development of pulsincap are shown in figure 4. Formula

TABLE 2 : Formula for pulsincap dosage forms

	F.NO	P1	P2	P3
	% of Ethyl cellulose solution used for coating of body of capsule	8%w/v	8%w/v	8%w/v
Hydrogel plug	Material used for preparation	gelatin	gelatin	gelatin
	Thickness	5mm	5mm	5mm
	Type of enteric polymer used for coating	cellulose acetate phthalate	hydroxy propyl Methyl cellulose phthalate	eudragit L-100
	% of enteric polymer used for coating	10%w/v	10%w/v	10%w/v

for different batches of pulsincap dosage forms were shown in TABLE 2.

Determination of physicochemical parameters of the pulsincap dosage forms

1. Determination of swelling efficiency of hydrogel plug

In this study, both full and half coated hydrogel plugs were taken in a 50ml of different pH buffers(i.e.6.8,and7.4).The hydrogel plugs were weighed before and after coating and at regular intervals(2,4,6,8,10,and 12 hrs). Swelling ratio can be find out by using the formula.

Swelling ratio=(weight of the hydrogel plug at 12hrs/weight of the hydrogel plug at zero time)

2. *In vitro* release studies of pulsincap[13]

Dissolution studies were carried out in a USP XXIII dissolution apparatus I, in 900ml medium at 37^0C at a rotation speed of 100rpm.

Depending on the GIT transit time and pH the formulated pulsincaps were tested at pH 1.2, 6.8 for 2hrs, 4hrs respectively and rest of the dissolution was carried out in pH 7.4 medium. At preset time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. The samples withdrawn were then filtered. The absorbance of the filtrate was determined at 318nm against respective dilution media as a blank.

3. Kinetic analysis of dissolution data[14]

The release profiles of indomethacin from different batches of microsponges and pulsincap dosage forms were fitted to different kinetic models such as zero order, first order, higuchi and peppas and hixson crowell to find the release pattern of drug from the formulations.

RESULTS AND DISCUSSION

Characterization of microsponges

Five batches of microsponge formulations containing different ratios of Indomethacin and ethyl cellulose[F1(1:1),F2(1.5:1), F3(2:1),F4(1:1.5)and F5(1:2)] were prepared and parameters like practical yield, percentage of drug content and percentage of encapsulation efficiency of microsponges were evaluated and given in TABLE 3.

TABLE 3 : Percentage of drug content and encapsulation efficiency of indomethacin microsponges

For. no	Drug: polymer ratio	Practical yield(g)	% of drug content	% of encapsulation efficiency
F1	1:1	0.8275	47.4	78.45
F2	1.5:1	1.0256	58.25	79.66
F3	2:1	1.3092	61.65	80.72
F4	1:1.5	1.0037	42.29	84.98
F5	1:2	1.2348	35.27	87.11

TABLE 4 : Mean particle size of indomethacin microsponges

S.No	Formulations	Average particle size(μm)
1	F1	79.8
2	F2	85.7
3	F3	93.1
4	F4	130.8
5	F5	157.8

The percentage of drug content in microsponges ranges from 35.27-61.65%. It decreases as the polymer concentration increases. The percentage of encapsulation efficiency increases with increase in polymer and drug concentrations. It was observed that percentage encapsulation efficiency increased more when polymer concentration was increased than when compared to the increase in drug concentration.

Mean particle size

The mean particle size of the prepared microsponges were determined and represented in figure 8. As the polymer concentration and drug concentration increases, the particle size increases. Increase in the particle size due to increase in the polymer concentration was more when compared to the particle size increase due to increase in the drug concentration. These results showed that the viscosity of internal phase was an important factor for the preparation of microsponges. The average values were given in TABLE 4.

Scaning electron microscopy

The scanning electron micrographs of batch F5 was taken and shown in the following GRAPH 2 Scanning electron microscopy indicated that the formulated microsponges are spherical and had smooth surface.

In vitro release studies of microsponges

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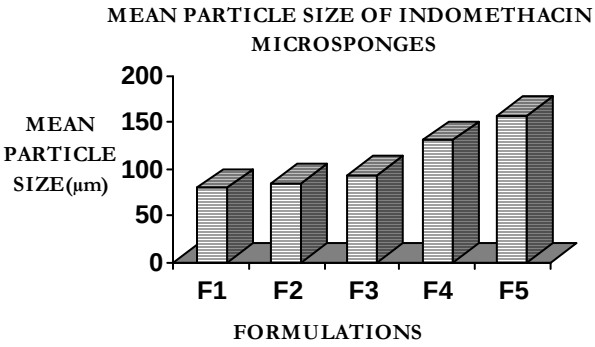
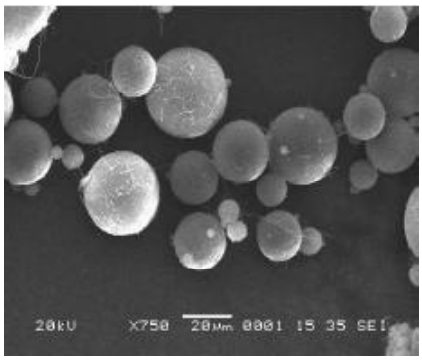
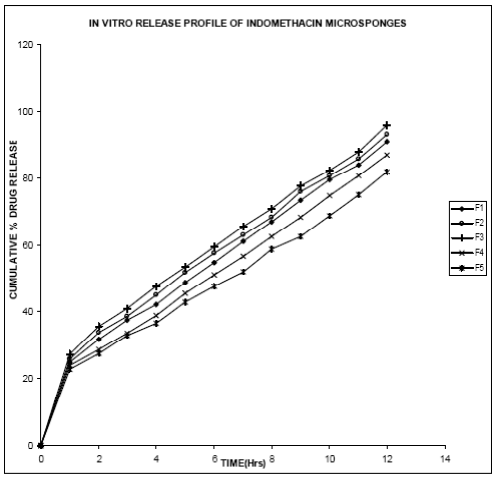


GRAPH 1



GRAPH 2



GRAPH 3

The *In vitro* dissolution profile of each prepared formulation was determined by using the dissolution apparatus U.S.P.X.XIII. (Paddle method). This study was carried out for a maximum period of 12hrs.

Comparative study of the dissolution profiles of the drug from different batches of microsponges prepared with various drug: polymer ratios were studied and tabulated in TABLE 5. The cumulative percentage of drug release was plotted against time. The

TABLE 5 : *In vitro* release profiles of indomethacin microsponges

Time (Hrs)	Cumulative % Drug release of Indomethacin microsponges*				
	F1	F2	F3	F4	F5
1	24.98±0.837	25.87±0.981	27.19±0.877	23.91±0.166	22.85±0.895
2	31.76±0.346	33.8±0.417	35.56±0.60	28.68±0.381	27.59±0.733
3	37.63±1.365	38.71±0.540	40.99±0.766	33.62±0.846	32.88±0.514
4	42.19±0.905	44.89±0.419	47.59±0.626	38.9±0.719	36.5±0.627
5	48.64±0.410	51.71±1.132	53.29±0.757	45.47±0.495	42.9±0.560
6	54.85±0.484	57.52±1.007	59.51±1.09	51.05±0.330	47.58±0.605
7	61.06±0.520	62.82±0.562	65.52±1.147	56.72±0.378	52±0.261
8	66.76±0.470	68.16±0.845	70.89±0.321	62.51±1.180	58.71±0.419
9	73.37±0.528	76.07±0.765	77.56±0.617	68.29±0.493	62.37±0.361
10	79.36±0.329	80.69±0.787	82.31±0.316	74.71±1.067	68.85±0.207
11	83.81±0.274	86.7±0.430	87.96±0.597	80.7±0.804	74.93±0.326
12	90.89±0.330	92.94±0.194	95.83±0.447	86.88±0.173	81.87±0.505

***Mean±Standard deviation**

drug release was shown in GRAPH 3.

The formulations F1, F2 and F3 released 90.78%, 92.82%, 95.89% at the end of 12th hr, whereas F4 and F5 have shown a maximum release of 86.69 % and 81.6% at the end of 12th hr. Therefore, F5 was selected as the best formulation for the development of pulsincap dosage form based on its controlled release nature and good encapsulation efficiency.

The *in vitro* release results showed that drug: polymer ratio influenced the release of drug from microsponges. On increasing the drug concentration the release of drug was increased and on increasing the polymer concentration drug release was decreased.

Determination of physicochemical parameters of the pulsincap dosage forms

1. Determination of swelling efficiency of hydrogel plug

From the results, the half enteric (10% CAP, 10% HPMCP and 10% Eudragit L-100) coated hydrogel plugs showed maximum swelling ratio 3.10,3.19 and 3.21 respectively in phosphate buffer pH 6.8 and are tabulated in TABLE 4.

It indicates that half coated hydrogel plugs in respect to its swelling characters(maximum swelling) suit the pulsincap dosage form when compared to full enteric coated hydrogel plugs. This also emphasizes that gelatin cap will get dissolved in stomach fluid, and the hydrogel plug swells in upper intestinal pH(6.8) resulting in ooping out of the capsule shell due to increase in volume. By the time it reaches to proximal colon it releases the microsponges from

TABLE 6 : Swelling characteristics of gelatin hydrogel plug

S no	Type of coating	Conc. of polymer (w/v)	Name of polymer	Wt.of dry hydrogel plug(mg)	Wt.of dry coated hydrogel plug(Ws)(mg)	PH	Wt.of swollen hydrogel plug at time "t" in hours(Ws)(mg)			Swelling ratio, R=Ws/Wd at 12 hrs
							2	8	12	
1	Full coated	5%	CAP	224	230	7.4	270	462	541	2.35
2	Full coated	5%	Eu L-100	217	225	7.4	311	375	449	1.99
3	Full coated	5%	HPMCP	221	233	7.4	268	358	429	1.84
4	Full coated	5%	CAP	215	231	6.8	261	396	463	2.01
5	Full coated	5%	Eu L-100	225	236	6.8	304	352	390	1.65
6	Full coated	5%	HPMCP	227	240	6.8	299	367	401	1.67
7	Full coated	10%	CAP	223	238	7.4	271	410	568	2.38
8	Full coated	10%	Eu L-100	209	218	7.4	306	368	401	1.83
9	Full coated	10%	HPMCP	231	241	7.4	332	425	504	2.09
10	Full coated	10%	CAP	235	242	6.8	295	426	543	2.24
11	Full coated	10%	Eu L-100	213	224	6.8	285	398	508	2.26
12	Full coated	10%	HPMCP	239	247	6.8	269	321	428	1.73
13	Half coated	5%	CAP	219	204	7.4	266	408	504	2.25
14	Half coated	5%	Eu L-100	221	229	7.4	318	453	545	2.37
15	Half coated	5%	HPMCP	220	216	7.4	291	469	576	2.54
16	Half coated	5%	CAP	218	227	6.8	283	484	567	2.49
17	Half coated	5%	Eu L-100	224	236	6.8	322	491	534	2.26
18	Half coated	5%	HPMCP	207	220	6.8	276	457	564	2.56
19	Half coated	10%	CAP	221	228	7.4	292	516	641	2.81
20	Half coated	10%	Eu L-100	228	237	7.4	308	530	622	2.62
21	Half coated	10%	HPMCP	214	224	7.4	283	509	620	2.76
22	Half coated	10%	CAP	223	234	6.8	316	623	743	3.21
23	Half coated	10%	Eu L-100	225	231	6.8	298	611	718	3.10
24	Half coated	10%	HPMCP	226	242	6.8	320	645	758	3.19

TABLE 7 : *In vitro* release profile of indomethacine from pulsincap dosage forms

Time(Hrs)	Cumulative % drug release of pulsincap dosage forms*		
	P1	P2	P3
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	8.64±0.563	4.86±0.421	1.98±0.452
8	19.75±0.836	18.06±0.417	13.9±0.325
9	25.83±0.561	23.76±0.521	19.7±0.408
10	31.96±0.459	29.75±0.303	27.75±0.690
11	40.87±0.372	36.6±1.340	33.62±0.650
12	46.74±0.667	44.86±0.511	41.14±0.808
13	51.87±0.843	49.84±0.5	48.85±0.263
14	57.12±0.539	55.33±0.297	54.42±1.258
15	63.42±0.750	61.68±0.85	60.98±0.779
24	92.78±0.964	91.65±1.058	90.9±1.505

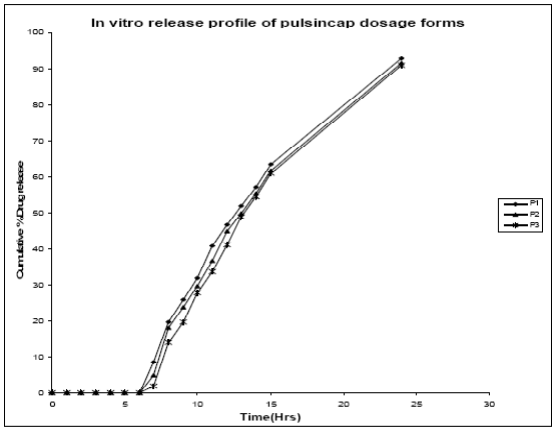
***Mean ± Standard deviation**

the dosage form to this area.

2. *In vitro* release studies of pulsincap dosage forms

The *in vitro* dissolution test was done in various pH media 1.2, 6.8, and 7.4 to simulate gastric, small intestine and colonic pH respectively. The formulations P1, P2, and P3 released 92.78%, 91.65% and 90.9% of drug for an extended period of 24hrs and the release profiles are shown in TABLE 7.

It indicates that all the dosage forms released the drug uniformly with out any significant difference. The cumulative percentage drug release was plotted against time. The graphical representation (GRAPH 4) revealed that drug release from the pulsincap dosage forms was started after 6hrs lag time i.e. no drug was released during usual



GRAPH 3

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TABLE 8 : Drug release kinetics of indomethacin mic5rosponges and pulsincap dosage forms

B.no	Higuchi	Zero order	First order	Korsmeyer-peppas	Hixson crowell
F1	0.9808	0.9651	0.922	0.9689	0.9665
F2	0.9855	0.961	0.9067	0.9798	0.9642
F3	0.9878	0.9546	0.8578	0.9786	0.9419
F4	0.9727	0.965	0.9325	0.9632	0.9705
F5	0.9717	0.9669	0.9378	0.9607	0.969
P1	0.8751	0.9452	0.8654	0.7652	0.9311
P2	0.8617	0.9422	0.8607	0.7609	0.9227
P3	0.8436	0.9325	0.8726	0.7395	0.9188

gastric(2hrs) and small intestine(3-4 hrs) transit time.

3. Kinetic analysis of dissolution data

The drug release rate kinetics data for all batches is shown in TABLE 8. The drug release data of all the microsponges were fitted to the Higuchi equation and pulsincap dosage forms fitted to the zero-order equation.

The prepared microsponges were characterized for particle size, SEM, entrapment efficiency and *In-vitro* release studies. Batch-F5 was selected for the development of pulsincap based on its sustained release. An 8%w/v ethyl cellulose solution was ideal for coating of body of the pulsincap, as the percentage change of weight was minimum. The prepared gelatin hydrogel plugs were full and half coated with different concentrations of enteric polymers. Half enteric(10% CAP, 10% HPMCP, and 10% EUDRAGIT L-100) coated hydrogel plugs were selected for development of pulsincap in respect to its maximum swelling ratio shown in pH 6.8 compared to the full enteric coated hydrogel plugs. In-vitro release studies were carried out for formulated pulsincaps. The release studies indicate that all the dosage forms released the drug uniformly with out any significant difference. The drug release from the pulsincap dosage forms was started after 6hrs lag time.

CONCLUSION

It could be concluded from the above investigation that pulsincap dosage form of Indomethacin could delay the release up to 6hrs and further exhibited controlled release of the drug for 18hrs.Hence it is suitable for the treatment of pain and inflammation caused by rheumatoid arthritis in early morning hours.

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REFERENCES

[1] Jayant Joshi, Prakash Kotwal; 'Essentials of Orthopaedics and applied Physiotherapy', Elsevier; 292-300 **(1999)**.
[2] Jason T.McConville; 'Recent trends in oral drug delivery', Drug delivery report, Mac carthy, India, **(2005)**.
[3] A.Akhgari, F.Sadeghi, H.Afrasiabi Garekani; Int.J.Pharm., **320**, 137-142 **(2006)**.
[4] D.M.Bramankar, B.Sunil Jaiswal; 'Biopharmaceutics, and Pharmacokinetics -Treatise', Vallabh Prakashan, **(1991)**.
[5] K.P.RChowdary, N.K.Rao, K.Malathi; Indian.J. Pharm.Sci., **66(4)**, 412-416 **(2004)**.
[6] Goodmann, Gilman's; 'The pharmacological basis of therapeutics', 9th edition, 705-706 **(2001)**.
[7] Geeta Patel, J.K.Patel; Indian Drugs, **45**, 12-14 **(2005)**.
[8] Pharmacopoeia of India: Controller of Publications, Ministry of Health, **2**, 142-144 **(1996)**.
[9] L.Lachman, H.Liberman, J.L.Kaing; The theory and Practice of Industrial Pharmacy, 3rd ed, 412-414 **(1989)**.
[10] D.Perumal; Int.J.Pharm., **218**, 1-11 **(2001)**.
[11] M.K.Chourasia, S.K.Jain; J.Pharm.Phamaceut.Sci., **6(1)**, 33-66 **(2003)**.
[12] Raymond C.Rowse, Paul J.Sheskey, Paul J.Welle; 'Hand book of Pharmaceutical Excipients', 3rd edition, American pharmaceutical association press, 237-240, 491-492 **(1994)**.
[13] FWu, ZR Zhang, WL He, Y Zhang; **37**, 733-8 **(2002)**.
[14] K.Rama, Prakash Senapati, M.K.Das; J.Microen capsul., **(22)**, 863-876 **(2005)**.
[15] Shweta Arora, J.Ali, Alaka Ahuja, Sanjula Baboota, J.Qureshi; Indian.Pharm.Sci., **68(3)**, 295-300 **(2006)**.