

Formulation and evaluation of mini-tablets-filled-pulsincap delivery of lornoxicam in the chronotherapeutic treatment of rheumatoid arthritis

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Abstract: In this present research work, we have designed a pulsincap formulation comprising mini-tablets, which to the best of our knowledge this combination has not been reported yet. We successfully combined the advantages of mini-tablets technology to meet the optimized requirements of our pulsincap formulation. Our main aim was to target lornoxicam to treat rheumatoid arthritis as per the chronotherapeutic pattern of the disease. Directly compressing method was used to prepare mini-tablets. The drug, polymers and combine mixtures of drug and polymers was evaluated for pre-formulation testing. Prepared mini-tablets were also evaluated for physicochemical, dissolution and stability studies. From FTIR and DSC evaluation, we found no interaction between the drug and polymers used. For mini-tablets, all the physico-chemical parameters were in limit. The mini-tablets of lornoxicam were filled into an insoluble body of capsule, and its opening was sealed by plugging it with a polymer. The complete capsule body after sealing with a cap was given enteric coating. Different polymers in various concentrations were used as a plug, to identify the most suitable which gives a complete lag time of 5 hours when combined with 5% CAP coating. HPMC-K100M in 30% and sodium alginate in 40% concentrations were identified as the most suitable plugs. Our optimized pulsincap formulations releases lornoxicam after a lag time of 5 hrs and maximum portion of the drug will be released in the early morning hours. It was also found to be stable for a period of 6 months as per ICH guidelines.

Keywords: Pulsincap formulation, mini-tablets, rheumatoid arthritis, chronotherapeutic pattern, lornoxicam.

INTRODUCTION

When it is desired to target the drug as per the circadian behaviour of diseases, then Pulsatile drug delivery technologies are most widely used. It means that these type of delivery systems will deliver the drug at time when disease shows it's most morbid and mortal state within a circadian cycle of 24 hours. This delivery system releases the drug in such a way that in the initial hours there will be no drug release followed by an immediate or controlled drug release. Thus, by the use of such approach drug can be delivered at the needed time, desired amount and at the accurate site (Anamika Singh *et al.*, 2012 and Survase *et al.*, 2007). In order to have a uniform therapeutic effect if a patient needs to have delayed absorption of drug, then targeting the drug to the colon would be useful. This type of conditions usually arises for diseases, which mainly persist during early morning hours like arthritis, asthma and angina etc. (Gothaskar AV *et al.*, 2004; Krishainah *et al.*, 2001).

Rheumatoid arthritis is considered as a chronic disease which mainly causes destruction in the integrity of joints. In patients with rheumatoid arthritis, symptoms such as joint stiffness and functional disability mainly persist in the early morning hours (Maurizio, 2012). These

symptoms are mainly characterized due to the diurnal variations in the levels of circulating pro-inflammatory cytokines, tumor necrosis factor- α and/or interleukin-6 (Arvidson *et al.*, 2007). It has been recommended to treat rheumatoid arthritis by using the concept of chronopharmacotherapy to ensure that the highest concentration of drug should be present in the bloodstream when the excessive stiffness and pain of the disease persist. However, drug delivery system would be more effective and useful when taken during midnight for targeting morning symptoms of rheumatoid arthritis than achieved by the same dose taken at early morning time. But, having patients awake at each midnight is clearly not an acceptable treatment option. (Frank Buttgerit, 2011). Therefore, we developed a novel pulsincap formulation to enable lornoxicam treatment with chronotherapeutic treatment of rheumatoid arthritis, in which the delivery of treatment is coordinated with biological rhythms.

Most of the literatures, which are available on pulsincap formulations were formulated by filling granules and pellets as multiple unit dosage forms. However, granules and pellets formulations do have a number of drawbacks. Controlling of size and size distribution of pellets or granules is a more critical factor during their preparation (Hong Wen and Kinam Park, 2011). Their size varies from formulation to formulation and within the formulation between the size range of 1 to 2 mm for

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pellets and 0.2 to 4.0 mm for granules (Aulton, 2000; Bechard and Leroux, 1992). Also, distribution of particle size has a strong effect on the dissolution rate profile of poorly soluble drugs. Because, if the particle is smaller the faster it will dissolve and if the particle is having a larger surface area the slower it dissolves. Therefore, to achieve a tight and reproducible release profile both a desirable pellet or granule size and a narrow particle size distribution are important and which is not easy to achieve because of their irregular shapes and sizes. Moreover, pellets and granules with different particle sizes and shapes have different flow properties during capsule filling which in turn affects the weight and drug content uniformity (Chu, 2012). When it comes to manufacturing the most widely used processes for the preparation of pellets are extrusion and spheronization, powder layering and solution or suspension layering. All of them require highly specialized equipments which makes the production process expensive in the pharmaceutical industry (Bechard and Leroux, 1992; Puniya Supriya *et al.*, 2012). For granules, the most widely used process is wet granulation method. In many processes of both the granules and pellets production it requires wetting and mechanical handling. Thus, the control of process often becomes difficult due to the amount of water added and time and in many cases over wetting may occur very easily. There will also be many chances for the loss of active material due to various stages of processing.

But, mini-tablets are very small tablets compared to normal tablets and they have uniform weights (25 mg), shapes and size distribution (circular shape and 3 mm size for all the batches) and it does not vary between formulations. Accurate measured amount of drug can be loaded in each mini-tablet. So, uniformity in drug content, weight and reproducible release profiles can be easily achieved. These mini-tablets also have a smaller size similar to granules and pellets. They can also be easily filled in capsules like other multiple unit dosage forms and can be modified in many ways for achieving the desired drug release profile. Their manufacture is very easy involving less number of steps during their preparation such as weighing, sieving, blending and compressing using 3 mm punches. Thus, saving the time and cost. Therefore, they resemble good substitutes for pellets and granules. (Carla Lopes *et al.*, 2006; Mohd Abdul Hadi *et al.*, 2012).

Lornoxicam possess potent analgesic and anti-inflammatory properties and comes under the class of NSAID's (Merck, 1996). This drug is widely used for the symptomatic treatment of inflammation and pain in rheumatoid arthritis and osteoarthritis patients (Kidd and Frenzel, 1996; Rainer *et al.*, 1996). Lornoxicam mechanism of action is based on decreasing prostaglandin synthesis by inhibition of cyclo-oxygenase enzymes as similar to other NSAIDs (Zhang *et al.*, 2005).

By keeping in view targeting lornoxicam during the time of its greatest need in the treatment of rheumatoid arthritis, we have developed a novel pulsincap formulation by utilizing the above-mentioned advantages of mini-tablets technology.

MATERIALS AND METHODS

Materials

Lornoxicam pure drug was received as a gift from IPS Pharma training institute, Hyderabad, A.P, India. HPMC K100M and PVP K 30[®] were obtained from FMC Biopolymer, Sodium carboxy methyl cellulose, sodium alginate, Lactose, Avicel[®] PH 102 and Aerosil[®] was purchased from SD Fine Chemicals, Mumbai, Magnesium stearate was purchased from Himedia Chem Lab, Mumbai. Cellulose acetate phthalate was purchased from Rajesh chemicals, Mumbai. Empty hard gelatin capsules (size '1') were obtained as a gift sample from ACG Associated capsules Pvt. Ltd. Mumbai. The remaining ingredients used were of analytical grade.

Preformulation studies

Fourier Transform Infrared (FTIR) spectral analysis

(Abanesh and Deshpande, 2013)

The pure drug lornoxicam and polymers used in this experimental work were studied for compatibility studies. We carried out these studies by taking 2 mg of sample in 200 mg of potassium bromide (Perkin Elmer, Spectrum-100, Japan). The range of scanning was 400-4000cm⁻¹ and resolution was 1cm⁻¹.

DSC studies

DSC thermograms of pure drug lornoxicam and physical mixture were recorded using Diffraction scanning calorimeter (DSC 60, Shimadzu, Japan). The measurement was performed between 30 and 350°C at heating rate 10°C/min.

Experimental methods

Preparation method used for cross-linking gelatin capsules (Mastiholimath VS *et al.*, 2007)

First, formalin vapours were generated by adding a pinch of potassium permanganate in a desiccator containing 25 ml of 15% (v/v) formaldehyde solution. Then the mesh containing about 100 empty bodies of hard gelatin capsules were exposed to these generated vapours of formaldehyde and the caps were left untreated in order to keep them water-soluble. Then this desiccator was tightly closed with a lid. In order to ensure that the capsule bodies should completely react with the formaldehyde vapours, the desiccator was kept aside for a period of 12 hours. After which the capsule bodies were taken out from the desiccator and dried at 50°C for 30 minutes and after capping with untreated caps were stored in a polythene bag.

Preparation of polymer plugs (Meena et al., 2011)

The polymer plugs which were used for plugging the opening of capsule bodies were prepared by direct compression technique by compressing polymer (Sodium carboxy methyl cellulose, HPMC-K100M, Sodium alginate) and lactose using 6 mm dies and punches on rotary tablet press (keeping constant thickness, weight and hardness values for all the hydrogel plugs).

Preparation of lornoxicam mini-tablets

(Noorana Tehseen et al., 2013)

Mini-tablets of lornoxicam were prepared as per the formula given in table 1. All ingredients (Drug lornoxicam, PVP K-30[®], Avicel[®] PH 102, Magnesium stearate and Aerosil[®]) were allowed to pass through a size 100 sieve, then weighed as per the required quantity and finally blended. This prepared blend after lubrication was finally compressed using directly compressing method, to weigh 25mg for each mini-tablet using 3mm round convex punches in a rotary tablet press (Rimek minipress, 10 station rotary machine, model RSB-4, M/s Karnavathi engineering Ltd, Ahmadabad).

Table 1: Composition of mini-tablet

S. No	Ingredients	Quantity (mg)
1	Lornoxicam	2
2	PVP K-30 [®]	1
3	Avicel [®] PH 102	21.5
4	Magnesium Stearate	0.25
5	Aerosil [®]	0.25
6	Total tab weight	25

Development of Pulsincap dosage form of lornoxicam

(Mastiholimath et al., 2007)

Four Mini-tablets equivalent to 8 mg of lornoxicam were filled by using hand into the formaldehyde exposed

capsule bodies. The opening of capsule bodies containing mini-tablets was then closed by plugging it with different polymers like sodium carboxy methylcellulose, HPMC-K100M and sodium alginate, separately at different concentrations (20, 30 and 40). Further, small amount of 5 % ethanolic solution of ethylcellulose was used to seal the joint between the capsule body and cap. These sealed capsule body and cap was then completely coated with 5 %w/w cellulose acetate phthalate in 8:2 (v/v) solution of acetone: ethanol which was plasticized with 0.75% of dibutylphthalate. Dip coating method was employed for coating the capsules. This coating was given in order to prevent variable gastric emptying. This procedure for coating was continued until 4-6% increase in weight of the total pulsincap formulation was obtained. Percentage weight gain of the capsules was determined after coating. Composition for preparing of pulsatile formulation is given in table 2.

Evaluation tests for capsules**Testing of formaldehyde exposed empty capsule bodies**

These capsule bodies after exposing to formaldehyde were tested for various characteristics such as changes in the dimension or any type of physical defects.

Disintegration studies for capsules

(Abraham et al., 2007)

First 10 empty capsules containing both untreated caps and treated bodies were randomly selected. Then the study was carried out by dipping and stirring a single capsule in different buffers of pH 1.2, 6.8 and 7.4 filled in disintegration apparatus. This testing was carried out at room temperature for a period of 24 hours.

Evaluation of polymer plugs (Leon Lachman and Herbert

Lieberman, 2009; Raghavendra et al., 2012)

The prepared polymer plugs was evaluated for hardness, thickness, weight variation and lag time.

Table 2: Composition of Pulsincap drug delivery system of Lornoxicam

FC	Weight of eight Mini-tablets used (mg)	Polymer used as a plug	Weight of polymer plug used (mg)		Weight of Empty capsule (mg) (size '1')	Total weight of the capsule (mg)	Weight of the capsule after CAP coating (mg)
			Polymer	Lactose			
F-1	101.2	NaCMC	20	80	96.4	297.6	308.5
F-2	100.4	NaCMC	30	70	96.5	296.9	308.5
F-3	102.0	NaCMC	40	60	96.5	298.5	310.7
F-4	100.5	HPMC-K100M	20	80	96.4	296.9	306.7
F-5	102.0	HPMC-K100M	30	70	96.3	298.3	309.9
F-6	101.7	HPMC-K100M	40	60	96.3	298.0	310.2
F-7	101.0	SA	20	80	96.4	297.4	308.6
F-8	102.5	SA	30	70	96.4	298.9	309.9
F-9	103.8	SA	40	60	96.4	300.2	311.6

*FC=Formulation Code, NaCMC=Sodium Carboxy Methyl cellulose, HPMC= Hydroxypropyl methylcellulose, SA= Sodium Alginate.

Note: Each pulsincap formulation comprises four mini-tablets, which is equivalent to 8 mg of lornoxicam.

Evaluation of mini-tablets

Pre-compression parameters (Leon Lachman and Herbert Lieberman, 2009; Raghavendra *et al.*, 2012)

Various pre-compressional parameters such as bulk and tapped density, Carr's compressibility index, Hausner's ratio and angle of repose were evaluated for the prepared powder blend of mini-tablets.

Post-compression parameters (Leon Lachman and Herbert Lieberman, 2009; Raghavendra *et al.*, 2012)

Various post-compressional parameters such as hardness, thickness, weight variation, friability etc. were evaluated for the prepared mini-tablets.

Drug Content Uniformity

For estimation of lornoxicam drug content first 10 mini-tablets were taken and then crushed into fine powder in the mortar. Then this fine powder equivalent to 8 mg of lornoxicam was extracted in pH 6.8 phosphate buffer. This solution was filtered through a Millipore filter of 0.45µm pore size. After suitable dilutions drug content was spectrophotometrically determined at a λ max of 375 nm.

In vitro dissolution testing of mini-tablets and pulsincap formulations (Gang *et al.*, 2004; Zahirul Khan *et al.*, 1999)

First, mini-tablets alone were evaluated for dissolution testing in 6.8 pH phosphate buffer for a period of 12 hours. Then, the pulsincap formulations were also evaluated for dissolution testing in three dissolution media i.e. 1.2, 7.4 and 6.8 pH for a period of 2, 3 and further 3 hours respectively. These three dissolution media are used to match the pH change criteria of the GI tract. The apparatus used for dissolution testing is USP-XXIII dissolution testing apparatus (i.e. basket type). In the first 2 hour, 750ml of pH 1.2 dissolution medium was used, and the test was subsequently continued in 900ml of medium at other pH conditions. Rotating speed of the basket in dissolution media was maintained at 100 rpm and the temperature was 37±0.5°C. At predetermined intervals of time 5ml of dissolution media was taken and replaced with fresh dissolution media. The withdrawn samples were analyzed at 376 nm, 377 nm and 375 nm respectively for 1.2, 7.4 and 6.8 pH buffers respectively by UV spectroscopic method and the mean cumulative percentage drug release was calculated over the sampling times.

Stability studies (Cha *et al.*, 2012; ICH Guidelines, 2003) Evaluation of optimized formulation for stability studies was carried out as per ICH guidelines at both room temperature and accelerated stability conditions. The conditions used for storing in room temperature were kept at 25±2°C and 65±5% RH and for accelerated stability were stored at 40±2°C and 75±5% RH in a humidity chamber. Firstly, stability of drug content was evaluated

for the mini-tablets. Secondly, after filling this mini-tablet, whole optimized pulsincap formulations were evaluated for dissolution studies in order to determine the effect of lag time on storage. Samples were withdrawn at equal intervals of for a period of 6 months and analyzed for appearance, drug content and dissolution profile.

RESULTS

FTIR and DSC studies

The FTIR spectral analysis (as shown in table 3 and fig. 1) showed that all the characteristic peaks remained intact in the spectra of physical mixtures of drug lornoxicam and polymers in pulsincap formulations.

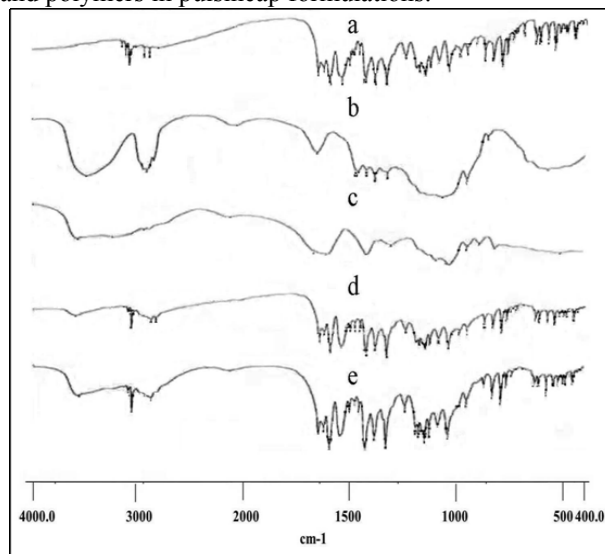


Fig. 1: FTIR spectra of a) Pure drug lornoxicam b) HPMC K100M c) Sodium alginate d) Lornoxicam+ HPMC K100M e) Lornoxicam+ Sodium alginate

During the present work, in addition to FTIR spectra of the drug and formulations DSC thermo gram analysis (as shown in fig. 2) has also not shown any chemical reaction.

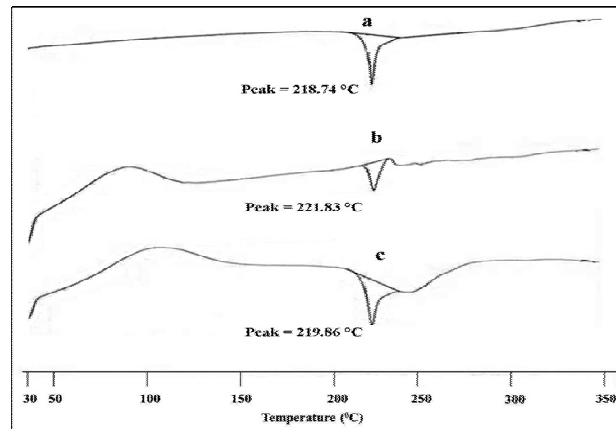


Fig. 2: DSC The rmograms of a) Pure drug lornoxicam b) Lornoxicam + HPMC K100M d) Lornoxicam + Sodium alginate.

Physical tests

It was found that the length and dimension of capsule bodies were found to decrease after formaldehyde treatment.

Disintegration studies for capsules

The untreated caps disintegrated within 9 minutes in all the media whereas the treated bodies remained intact for about 24 hours.

Evaluation of polymer plugs

Various physico-chemical properties of the polymer plugs were evaluated and were found to be limits. The results are shown in table 4.

Evaluation of prepared powder blend

Various micrometric properties of the prepared powder blend was evaluated and was found to exhibit good flow properties as evident from the results in table 5.

Evaluation of prepared mini-tablets

Various physico-chemical properties of prepared mini-tablets were evaluated and were found to be limits. All these results have been shown in table 6.

In vitro dissolution studies of mini-tablets and pulsincap formulations

The *in vitro* dissolution studies were performed for both mini-tablets and pulsincap formulations. The % cumulative release of all batches is shown in (fig. 3-6).

Table 3: Results of FTIR studies

Functional group	Peak in pure drug lornoxicam	Peak in HPMC K100M polymer	Peak in Sodium alginate polymer	Peak in lornoxicam + HPMC K100M physical mixture	Peak in lornoxicam + sodium alginate physical mixture
Ar-CH	3100 cm ⁻¹ (Stretching)	--	--	3104 cm ⁻¹ (Stretching)	3101 cm ⁻¹ (Stretching)
-NH	3066 cm ⁻¹ (Stretching)	--	--	3068 cm ⁻¹ (Stretching)	3067 cm ⁻¹ (Stretching)
-C=O	1647 cm ⁻¹ (Stretching)	--	--	1649 cm ⁻¹ (Amide Stretching)	1646 cm ⁻¹ (Amide Stretching)
-CONH-	1594 cm ⁻¹ (Secondary amide Bending)	--	--	1595 cm ⁻¹ (Secondary amide Bending)	1594 cm ⁻¹ (Secondary amide Bending)
-SO ₂	1327 cm ⁻¹ (Bending)	--	--	1328 cm ⁻¹ (Bending)	1327 cm ⁻¹ (Bending)
C-Cl	790 cm ⁻¹ (Bending)	--	--	790 cm ⁻¹ (Bending)	790 cm ⁻¹ (Bending)
-OH	--	3470 cm ⁻¹ (Stretching)	3567 cm ⁻¹ (Stretching)	3595 cm ⁻¹ (Stretching)	3565 cm ⁻¹ (Stretching)
-CO	--	1375 cm ⁻¹ (Bending)	1302 cm ⁻¹ (Bending)	1383 cm ⁻¹ (Bending)	1381 cm ⁻¹ (Bending)
-CH	--	2839 cm ⁻¹ (Stretching)	2943 cm ⁻¹ (Stretching)	2880 cm ⁻¹ (Stretching)	2881 cm ⁻¹ (Stretching)

Table 4: Evaluation of polymer plugs

Polymer plug code	Polymer used	Average weight (mg) (±SD), n=20	Thickness (mm) (±SD), n=6	Hardness (kg) (±SD), n=6
PP-1	NaCMC (20mg)	100.08±0.557	3.21±0.011	2.56±0.025
PP-2	NaCMC (30mg)	100.38±1.151	3.20±0.023	2.56±0.017
PP-3	NaCMC (40mg)	101.04±0.616	3.21±0.015	2.59±0.041
PP-4	HPMC-K100M (20mg)	98.53±0.435	3.20±0.017	2.57±0.037
PP-5	HPMC-K100M (30mg)	100.57±1.024	3.20±0.005	2.53±0.023
PP-6	HPMC-K100M (40mg)	99.77±0.210	3.21±0.011	2.58±0.045
PP-7	Sodium alginate (20 mg)	100.02±0.541	3.21±0.010	2.55±0.055
PP-8	Sodium alginate (30 mg)	100.21±0.291	3.21±0.011	2.57±0.011
PP-9	Sodium alginate (40 mg)	99.79±0.687	3.20±0.005	2.56±0.023

Table 5: Results of physical evaluation of pre-compression blend

Batch	Angle of repose (°) ± SD, n=3	Bulk density (gm/cc) ± SD, n=3	Tapped density (gm/cc) ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's ratio ± SD, n=3
Mini-tablets powder blend	22°.58'±0.437	0.52 ± 0.0157	0.59 ± 0.005	11.86 ± 1.08	1.13 ± 0.022

Table 6: Evaluation of mini-tablets

Batch	Average weight (mg) (±SD), n=20	Hardness (kg) (±SD), n=6	Thickness (mm)(±SD), n=6	Friability (%) (±SD), n=6	% Drug content (±SD), n=3
Mini-tablets	24 ± 0.146	2.15 ± 0.005	2.09±0.083	0.54 ± 0.041	98.19± 0.170

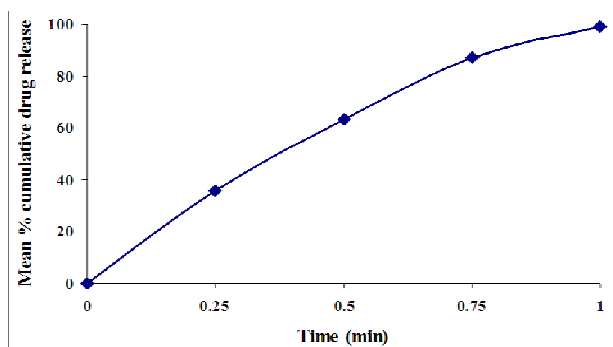


Fig. 3: *In vitro* release profile of mini-tablets batch

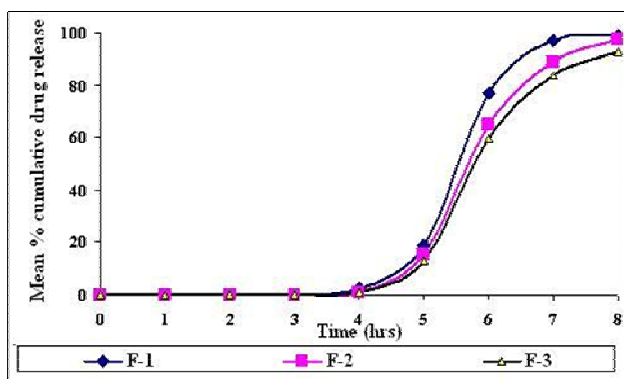


Fig. 4: *In vitro* release profile of pulsincap formulations containing NaCMC as a polymer plug

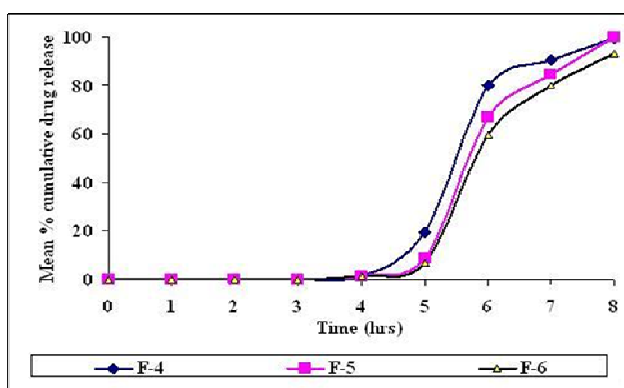


Fig. 5: *In vitro* release profile of pulsincap formulations containing HPMC-K100M as a polymer plug

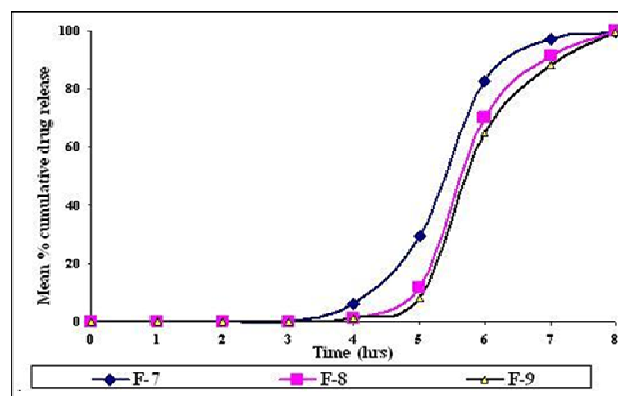


Fig. 6: *In vitro* release profile of pulsincap formulations containing Sodium alginate as a polymer plug

Stability studies

The stability study was performed for a period of 6 months and was found there not any significant changes to the physical appearance, drug content and dissolution profiles.

DISCUSSION

We have mentioned in the introduction, our main was to target lornoxicam as per the circadian rhythm of rheumatoid arthritis. As the symptoms of this disease mainly persists in the early morning hours, by keeping this fact in view we aimed to design a novel pulsincap formulation. The desired lornoxicam release profile was targeted in such a way that it should release lornoxicam after a lag time (i.e. less than 10%) of minimum 5 hours and maximum portion of the drug should be released between 6 to 8 hours. This target release profile is based on the assumption that if the patient takes our prepared optimized formulation at 10:00 P.M in the night (i.e. before going to bed), then the drug starts releasing from 3:00 A.M and maximum portion of the drug will be available between 4-6 A.M. Hence, maximum portion of the drug will be released in the early morning hours for better treatment of rheumatoid arthritis as per chronotherapy.

The device was formulated in three steps: Firstly, lornoxicam was prepared as mini-tablets; secondly lornoxicam mini-tablets were filled in a non-disintegrating capsule body, and its opening was closed by plugging it with a polymer, which was joint with a cap by sealing; thirdly the complete capsule was enteric coated with pH dependent polymer i.e cellulose acetate phthalate.

FTIR and DSC studies

Spectra of pure drug Lornoxicam, polymers and physical mixture of all these in mini-tablets and pulsincap formulations was recorded in between 400 to 4000 cm^{-1} . The FTIR spectral analysis showed that all the characteristic peaks remained intact in the spectras of physical mixtures of drug lornoxicam and polymers in pulsincap formulations.

During the present work in addition to FTIR spectra of the drug and formulations DSC thermo gram analysis was also used for studying physical characteristics & for the characterization of the drug and formulations. DSC thermo gram of lornoxicam due to its melting process shown a sharp endothermic peak at 218.74°C. The peak for physical mixture of lornoxicam and HPMC-K100M in pulsincap formulation F-5 was found at 221.83°C. Whereas, the peak for physical mixture of lornoxicam and sodium alginate in formulation F-9 was found at 219.86°C. Hence, the same range of pure drug melting peak is present even in the physical mixture of formulations. Thus, it is an indication that drug and polymers have not undergone any chemical reaction.

Physical tests

When 100 capsules were taken for formaldehyde treatment, out of them some 13 capsules were found to be shrunk or distorted. The variation in dimensions were also studied by measuring the formaldehyde treated and untreated capsules. It was found that the length and dimension of capsule bodies were found to decrease after formaldehyde treatment.

Disintegration studies for capsules

When the capsules were subjected to disintegration studies in different buffers, the untreated caps disintegrated within 9 minutes in all the media whereas the treated bodies remained intact for about 24 hours. This is due to the reason that formal in exposure resulted in decreased solubility of gelatin.

Evaluation of polymer plugs

In order to have a tight fitting at the opening of the impermeable capsule body and to prevent the penetration of buffer into the capsule various polymer plugs were designed. We used same thickness, weight and hardness for all the polymer plugs, in order to evaluate the effect of increased concentration of polymer in the plugs. Various

physico-chemical properties were evaluated. The results are shown in table 4.

Evaluation of prepared powder blend

The value for angle of repose was found to be 22.58 ± 0.437 which was less than 30 and hence indicates good flow properties of the powder blend. The value of compressibility index was found to be $11.86 \pm 1.08\%$ which was less than 15% and hence this too indicates good to excellent flow properties. The results of Hausner's ratio were also found to be lesser than 1.25 which indicates better flow properties. Thus, the prepared powder blend was found to exhibit good flow properties.

Evaluation of prepared mini-tablets

The values for hardness and friability of the mini-tablets was found to be $2.15 \pm 0.005\text{kg}$ and $0.54 \pm 0.041\%$ respectively. The hardness was found to be uniform and the friability value was also found to be less than 1. Thus, these two parameters indicate that mini-tablets have got sufficient strength. The value for average weight was found to be $24 \pm 0.146\text{mg}$. The Pharmacopoeial limit for % deviation of tablets of 130 mg or less is $\pm 10\%$ and all the mini-tablets were found to pass as per the specifications given in Indian pharmacopoeia for weight variation test. The drug content was found to be $98.19 \pm 0.170\%$ and thus it was also complying with the specifications i.e. not less than 95%.

In vitro dissolution studies of mini-tablets and pulsincap formulations

Our aim was to have an immediate release of lornoxicam from the mini-tablets in the colon after a lag time of minimum 5 hours. So, we have not incorporated any polymer in the composition of mini-tablets. The mini-tablets were used just to increase the bulk volume of lornoxicam by using Avicel[®] PH 102a fast dissolving diluent. They were also used due to their more uniformity in weights (25 mg), shapes (circular), sizes (3 mm), drug content (more than 98 %) and their easy preparation. In dissolution studies, first mini-tablets alone were subjected for evaluation in 6.8pH phosphate buffer. From the dissolution studies of mini-tablets batch it was found that they released $99.10 \pm 0.96\%$ of lornoxicam upto 1 hour.

The prepared pulsincap formulations containing mini-tablets plugged with different polymers were also subjected to dissolution testing. Our main aim in this dissolution testing was to identify a suitable concentration and type of polymer plug which when combined with 5% CAP coating on entire capsule releases the drug (less than 10%) after a lag time of 5 hours. It means 5% CAP coating should prevent the release of lornoxicam in stomach i.e. 1.2pH medium and further polymer plug should prevent the release of lornoxicam in small intestine i.e. 7.4 pH phosphate buffer saline (PBS) and should release lornoxicam only in colonic medium i.e. 6.8 pH dissolution medium.

In all the formulations it was found that 5% coating of cellulose acetate phthalate to the hard gelatin capsules was sufficient to retard the drug release for 2 hours in 1.2 pH, but the coating could not withstand in small intestinal fluid, and thus the cap was released from the capsule body. The release of the drug from the pulsincap formulations was found to be dependent upon the concentration of plug. It was found that when the polymer concentration in the plug increased it resulted in decreased drug release. It is due to the reason that the plugged polymer after absorbing the surrounding dissolution medium, has completely swelled and formed a swollen matrix and after wetting became a soft mass and came out of the capsule body. Thus, it resulted in the release of lornoxicam incorporated mini-tablets. Only in the initial 2 hours the release will be pH dependent due to enteric coating and in further remaining hours it becomes time dependent due to hydrophilic polymer plugs present at the opening of the capsule body. The two pH buffer systems (pH 7.4 and pH 6.8) were used only to maintain the conditions of the small intestine and colon and they did not have any effect on the drug release mechanism.

When formulations F-1, F-2 and F-3 prepared with sodium carboxy methyl cellulose as a polymer plug were subjected to dissolution studies, it was found that around 18.60±0.42, 15.14±0.45, 12.87±0.67% of lornoxicam was released upto 5 hours and 99.22±0.61, 99.79±0.59, 93.02±0.29% of lornoxicam was released upto 8 hours respectively.

When formulations F-4, F-5 and F-6 prepared with HPMC-K100M as a polymer plug were subjected to dissolution studies, it was found that around 19.31±0.26, 8.58±0.93, 6.91±0.70% of lornoxicam was released upto 5 hours and 99.58±0.58, 99.97±0.43, 91.02±0.65% of lornoxicam was released upto 8 hours respectively.

When formulations F-7, F-8 and F-9 prepared with sodium alginate as a polymer plug were subjected to dissolution studies, it was found that around 29.57±0.33, 11.68±0.15, 7.99±0.75% of lornoxicam was released upto 5 hours and 99.46±0.56, 99.93±0.42, 99.69±0.37% of lornoxicam was released upto 8 hours respectively.

In all these formulations, formulation F-5 containing HPMC-K100M as a polymer plug in 30 mg concentration and formulation F-9 containing Sodium alginate in 50 mg concentration as a polymer plug was considered to be the most suitable plug as it released minimum percentage of lornoxicam i.e. less than 10% upto 5 hours. Our aim was also the same, to release lornoxicam after a lag time of minimum 5 hours. Thus, when these formulations are administered at bedtime i.e. 10:00 PM, then the drug starts releasing from 3:00 A.M and hence maximum portion of the drug will be released in between 4-6 A.M at which the symptoms of Rheumatoid arthritis are at its peak.

Stability studies

When optimized pulsincap drug delivery systems (F-5 and F-9) were stored at both the conditions during a period of 6 months it was found that there was not any change in appearance for both mini-tablets and capsule shell. During the evaluation of drug content, it was found that the amount of lornoxicam was reduced by 0.85% at room temperature and 0.74% at accelerated stability conditions (i.e less than 1%) in a period of 6 months suggesting that the drug was stable. When stability studies were performed for in-vitro release profile it was observed that there was very small variation (i.e. less than 1%) in both lag time and drug release profile for the optimized formulations at both conditions. Thus, by the above mentioned results it was confirmed that our optimized formulations were stable for a period of 6 months.

CONCLUSION

Novel pulsincap formulations were successfully developed by filling of mini-tablets in a capsule body. The capsule body containing mini-tablets after plugging with a polymer, and sealing with a cap was completely enteric coated with 5% w/w cellulose acetate phthalate. Formulation F-5 and F-9 was considered as the best formulations as they shown a complete lag time of 5 hours and released 99.97±0.43, 99.69±0.37% at the end of 8 hours respectively. Thus, mini-tablets-filled pulsincap formulations of lornoxicam can be suitable for optimum colonic delivery of lornoxicam in the treatment of rheumatoid arthritis as per chronotherapy.

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