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Research Article

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM CONTAINING INDOMETHACIN USING NATURAL POLYMERS

Kamat Akshay Ramesh*, Shabaraya A. R., Azharuddin Mohd., Krishnananda Kamath K.
Dept. of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Post Parengipete, Mangalore, India

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*Email: akshay.kamat1989@gmail.com

ABSTRACT
Aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system using natural superdisintegrants and natural polymers to achieve time release of Indomethacin, based on chronopharmaceutical approach for the treatment of rheumatoid arthritis. Pulsatile delivery system is capable of delivering drug when and where it required most. By administering the system at bedtime, but releasing drug as a burst after the lag time (during peak morning hours) thereby delivering the drug when and where it is required the most with decreased side effects, dose size and prolonged action. The press-coated pulsatile release tablet contains Indomethacin in the inner rapid release core tablet formulated by direct compression method using plantago ovata mucilage and modified agar as superdisintegrants and the external coat formulated using natural polymers such as dammar gum, chitosan, xanthan gum and gaur gum by both direct and wet granulation method. The prepared press-coated pulsatile tablets were evaluated for various pre-compressional and post-compressional parameters. *In-vitro* release profiles of pulsatile device during 10 h studies were found to have very good sustaining efficacy. Formulation code A1, A8, B2 and B7 were selected as the best formulations with formulation B2 containing xanthan gum and dammar gum in the ratio 2:1 having maximum lag time of 7 h 15 min.
Keywords: Pulsatile drug delivery system, natural polymers, rheumatoid arthritis, rupture test, lag time.

INTRODUCTION

In the present study, attempt was made to develop a suitable pulsatile drug delivery system for effective treatment of rheumatoid arthritis (RA) depending on the chronobiology of the disease. RA is characterized by the prominent feature of morning stiffness which occurs at peak early morning hours and the pain in joints decreases as the day goes on with less or no pain at night.

A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system for the effective treatment of RA[1,2].

Polymers have been successfully investigated and employed in the formulation of various dosage forms and are specifically useful in the design of novel drug delivery systems. Synthetic polymers are toxic, expensive, have environment related issues, need long development time for synthesis and are freely available in comparison to naturally available polymers. However the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic and capable of chemical modifications, potentially biodegradable and with few exceptions and also biocompatible[3,4,5,12].

In the present study the natural polymers that were selected as suitable candidates for PDDS are: Dammar gum (DG), xanthan gum (XG), gaur gum (GG) and chitosan.

MATERIAL AND METHOD

Indomethacin (IM), agar agar, xanthan gum and chitosan were purchased from Yarrow Chemicals, Mumbai. Gaur gum was purchased from Loba chemie Mumbai. Psyllium seeds were purchased from central market Humpankatta, Mangalore. Dammar gum was obtained as gift sample from M. S. Mansukhlal and Co., Mumbai. All the other excipients used in the study were of analytical grade.

Isolation of mucilage from Psyllium seed[7]

The Psyllium seeds were soaked in distilled water for 48 h and then boiled for 10 min. The resulting mass was squeezed through muslin cloth. To the filtrate an equal volume of acetone was added to precipitate the mucilage. The isolated mucilage was dried in an oven at 40°C for 2 h, powdered, passed through sieve no.80 and stored in a dessicator.

Preparation of Modified Agar (MA)[8]

Modification of natural agar was done by suspending 5gm of Agar agar in 100 ml of distilled water. The suspension is stirred at 500 rpm using magnetic stirrer for 24 hrs. Obtained swollen mass is dried at 40°C for 72 h. Dried product is collected and crushed in pestle mortar and passed through sieve no.100.

Preparation of rapid release core tablets (RRCTs) of IM[6]

The rapid release core tablets were prepared using a KBr hydraulic press with suitable flat punches. The core was made of the suitable mixture of powder blends of IM, Microcrystalline Cellulose (MCC, Avicel pH-102), Psyllium Seeds mucilage, MA and starch. Eight formulations were prepared; Formulation RRCT1, RRCT2, RRCT3, RRCT4 containing 4%, 6%, 8% and 10% of Psyllium Seeds mucilage as superdisintegrant respectively. Formulation RRCT5, RRCT6, RRCT7, RRCT8 containing 4%, 6%, 8% and 10% of MA as superdisintegrant respectively. All above ingredients in each formulation batch were dry blended for 20 min followed by addition of Magnesium Stearate. The mixture was then further blended for 10 min. 120 mg of the resultant mixture was directly compressed at a pressure of 1 ton for 1 min using 9 mm punch and die.

Coating of the RRCTs[6]

Formulation of Powder blend for press-coated tablets prepared by direct compression method

Powder blend for press-coated tablet was prepared by dry blending together different compositions of the XG, GG, DG and Chitosan. These excipients were dry blended in different weight compositions in order to get suitable polymer composition. This composition is dry blended until uniformly blended mixture is obtained. This mixture is then used for the preparation of press-coated tablet using direct compression method; formulation codes A1-A12.

Formulation of barrier layer granules for press-coated tablets prepared by wet granulation method

A wet granulation process was used to prepare the barrier

layer granules. The compositions of XG, GG, DG, Chitosan were wet granulated using polivinylpyrrolidone (PVP, K90) as binder. 5% granulating solvent system was made by dissolving PVP into hot water by continuous stirring. The dump mass was prepared and passed through sieve no.18 to obtain the granules. The granules were dried in hot-air oven at about 40°C for 24 h and stored in airtight container and used as press-coating material to prepare press-coated pulsatile tablets; formulation codes B1-B12.

Formulation of press-coated pulsatile tablets by direct compression and wet granulation method

The core tablets were press-coated with 300 mg of powder blend/granules. 150 mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the centre. The remaining 150 mg of the barrier layer material was added into the die and compressed at a pressure of 2 tons for 1.5 min using KBr hydraulic press.

Evaluation of rapid release core (RRCT) and press-coated tablets of IM

Weight variation[6,10]**:** Twenty tablets were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated**.**

Thickness[6,10]**:** Three tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of Vernier caliper. The average thickness was calculated.

Hardness[6,10]**:** Hardness was measured using Monsanto tablet hardness tester. The hardness of five tablets in each batch was measured and the average hardness was calculated in terms of kg/cm^2.

Friability (F)[6,10]**:** Friability of the tablet determined using Roche friabilator. Pre-weighted sample of tablets were placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

Wetting time[9]**:** Wetting time of dosage form is related to the contact angle. A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. Tablet was kept on the paper and the time for complete wetting was measured. The mean ± SD values were calculated accordingly.

Drug content[6,9]**:** For determination of drug content at least five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer of pH 6.8 in a volumetric flask. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 318 nm against blank. Drug content was calculated using standard curve.

Disintegration time for RRCTs[9]**:** LABINDIA DT 1000 USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing phosphate buffer pH 7.2 at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

***In-vitro* release studies for RRCTs**[6,9]

Tablet was introduced into the basket of the LABINDIA TS 8000 USP dissolution test apparatus and the apparatus was set in motion at 50 rpm for time period of 3 hrs, 5 ml of sample was withdrawn for 1st hr at 15 min intervals and after that at 30 min intervals and replaced by pH 7.2 phosphate buffer solutions. Samples withdrawn were analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

***In-vitro* Dissolution methods for press-coated tablets**[9,10]**:** Dissolution testing of Pulsatile delivery systems with the conventional paddle method at 100 rpm and 37±0.5°C been conducted in phosphate buffer pH 7.2. The samples were withdrawn at regular intervals and analyzed by UV spectrophometer (Shimadzu UV/Vis 1800) for the presence of the drug.

Stability Studies[11]**:** The stability study of the formulations A1, A8, B2 and B7 was carried out according to ICH guidelines at 40 ± 2°C/75 ± 5 % RH for one month by storing the samples in stability chamber (Lab-care, Mumbai).

TABLE 1: COMPOSITION OF RRCT OF IM

Ingredients (mg)	RRCT1	RRCT2	RRCT3	RRCT4	RRCT5	RRCT6	RRCT7	RRCT8
IM	75	75	75	75	75	75	75	75
MCC	27.2	24.8	22.4	20	27.2	24.8	22.4	20
Psyllium Seeds mucilage (%)	4 %	6 %	8 %	10 %	-	-	-	-
Modified Agar (%)	-	-	-	-	4 %	6 %	8 %	10 %
Starch	12	12	12	12	12	12	12	12
Magnesium Stearate	1	1	1	1	1	1	1	1
Total Weight	120	120	120	120	120	120	120	120

TABLE 2: FORMULATION OF PRESS-COATED TABLETS BY DIRECT COMPRESSION AND WET GRANULATION METHOD

Ingredients (mg)	A1/B1 (1:1)	A2/B2 (2:1)	A3/B3 (1:2)	A4/B4 (1:1)	A5/B5 (2:1)	A6/B6 (1:2)	A7/B7 (1:1)	A8/B8 (2:1)	A9/B9 (1:2)	A10/B10 (1:1)	A11/B11 (2:1)	A12/B12 (1:2)
RRCT	120	120	120	120	120	120	120	120	120	120	120	120
XG	150	200	100	-	-	-	150	200	100	-	-	-
DG	150	100	200	-	-	-	-	-	-	150	200	100
GG	-	-	-	150	200	100	-	-	-	150	100	200
Chitosan	-			150	100	200	150	100	200	-	-	-
Total Weight	420	420	420	420	420	420	420	420	420	420	420	420

TABLE 3: EVALUATION OF RRCTs

Formulation code	Thickness* (cm)	Hardness** (kg/cm^2)	Average weight*** (mg)	Friability* (%)	Drug content** (%)	Disintegration time* (sec)	Wetting time* (sec)
RRCT1	0.448±0.006	2.22±0.020	119.48±0.206	0.6204±0.0353	92.10	41.3±2.08	149.6±2.08
RRCT2	0.452±0.002	2.25±0.020	118.96±0.133	0.6029±0.0455	94.45	38±2.64	120.3±2.51
RRCT3	0.450±0.006	2.23±0.020	119.61±0.280	0.5818±0.0219	97.29	32.6±2.30	79±3.00
RRCT4	0.444±0.001	2.25±0.020	119.63±0.130	0.6253±0.0402	98.85	30±1.73	49.6±3.21
RRCT5	0.453±0.003	2.30±0.015	119.66±0.378	0.6007±0.0401	90.34	45.6±2.88	295.3±2.51
RRCT6	0.449±0.001	2.23±0.025	119.87±0.095	0.6264±0.0422	93.18	43.3±2.51	245.6±1.52
RRCT7	0.451±0.006	2.25±0.020	118.92±0.156	0.6198±0.0369	95.66	39.3±2.30	179.3±2.30
RRCT8	0.450±0.005	2.23±0.020	119.44±0.445	0.6268±0.0288	97.13	35.3±1.15	116.3±2.08

Mean ± S.D., n= 3, 5**, 20***

TABLE 4: STABILITY STUDIES OF SELECTED BATCHES OF PRESS-COATED TABLETS

Formulation code	Hardness test* (kg/cm^2)		Friability** (%)		Average weight*** (mg)		Thickness** (mm)		Drug content* (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After
A1	5.54±0.025	5.44±0.019	0.6974±0.0197	0.7011±0.0185	419.78±0.22	418.44±0.15	0.611±0.003	0.604±0.002	98.85 ±0.56	97.56 ±0.25
A8	5.59±0.036	5.38±0.022	0.7015±0.0241	0.7123±0.0168	419.77±0.25	418.51±0.18	0.602±0.003	0.591±0.004		
B2	6.51±0.023	6.34±0.016	0.7025±0.0108	0.7172±0.0102	421.38±0.30	420.42±0.21	0.605±0.002	0.594±0.003		
B7	6.77±0.025	6.52±0.018	0.7274±0.0170	0.7312±0.0158	420.32±0.20	419.08±0.16	0.604±0.002	0.593±0.002		

All values are expressed as mean ± SD, n=5*, 3**, 20***.

TABLE 5: EVALUATION OF PRESS-COATED PULSATILE TABLETS DIRECT COMPRESSION BATCHES

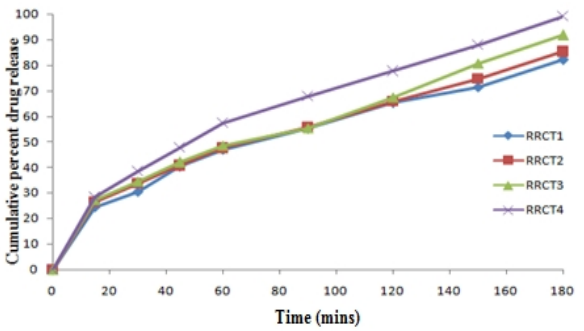
Formulation code	Thickness (cm)	Hardness (kg/cm^2)	Average weight (mg)	Friability (%)
A1	0.611±0.003	5.54±0.025	419.78±0.22	0.6974±0.0197
A2	0.608±0.002	5.51±0.030	419.67±0.29	0.7025±0.0253
A3	0.604±0.004	5.58±0.030	421.05±0.17	0.7183±0.0229
A4	0.614±0.004	5.53±0.020	419.92±0.14	0.6969±0.0175
A5	0.617±0.003	5.62±0.030	419.46±0.23	0.6965±0.0227
A6	0.615±0.003	5.54±0.035	419.28±0.35	0.6970±0.0152
A7	0.605±0.004	5.55±0.026	420.02±0.15	0.7083±0.0123
A8	0.602±0.003	5.59±0.036	419.77±0.25	0.7015±0.0241
A9	0.612±0.003	5.46±0.036	421.07±0.14	0.7023±0.0197
A10	0.610±0.002	5.60±0.025	419.19±0.30	0.6902±0.0243
A11	0.603±0.004	5.43±0.035	419.32±0.38	0.7019±0.0233
A12	0.606±0.003	5.50±0.037	420.01±0.13	0.7043±0.0152

*Mean ± S.D., n= 3

TABLE 6: EVALUATION OF PRESS-COATED PULSATILE TABLETS WET GRANULATION BATCHES

Formulation code	Thickness (cm)	Hardness (kg/cm^2)	Average weight (mg)	Friability (%)
B1	0.612±0.002	6.66±0.020	419.39±0.33	0.7205±0.0131
B2	0.605±0.002	6.51±0.023	421.38±0.30	0.7025±0.0108
B3	0.613±0.003	6.80±0.025	420.66±0.31	0.6930±0.0132
B4	0.614±0.002	6.76±0.030	419.29±0.29	0.7046±0.0152
B5	0.602±0.006	7.25±0.025	421.41±0.32	0.7193±0.0136
B6	0.617±0.003	7.34±0.036	420.68±0.27	0.7141±0.0157
B7	0.604±0.002	6.77±0.025	420.32±0.20	0.7274±0.0170
B8	0.606±0.001	6.67±0.030	419.20±0.17	0.7393±0.0171
B9	0.609±0.002	7.59±0.035	419.40±0.23	0.7155±0.0163
B10	0.606±0.005	6.30±0.030	421.41±0.19	0.7249±0.0151
B11	0.603±0.002	7.22±0.023	421.48±0.26	0.6917±0.0174
B12	0.615±0.004	7.34±0.035	420.52±0.22	0.6933±0.0137

*Mean ± S.D., n= 3



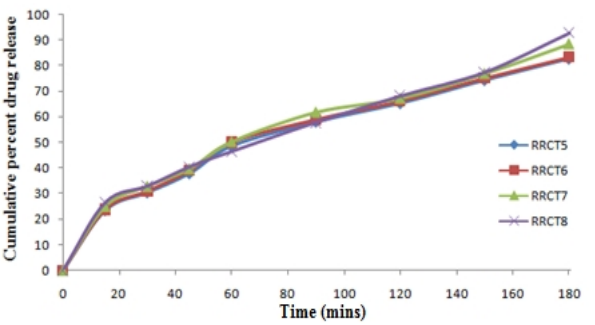
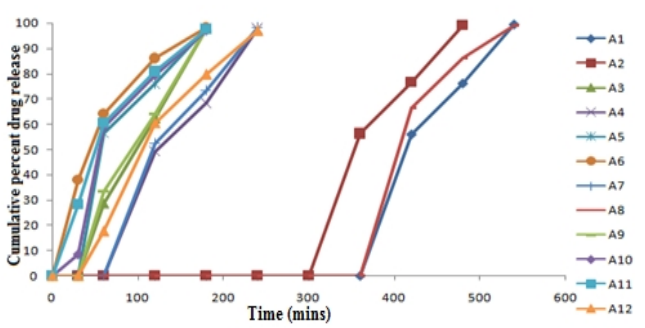


Figure 1 and Figure 2: *In-vitro* dissolution profiles of RRCT formulations



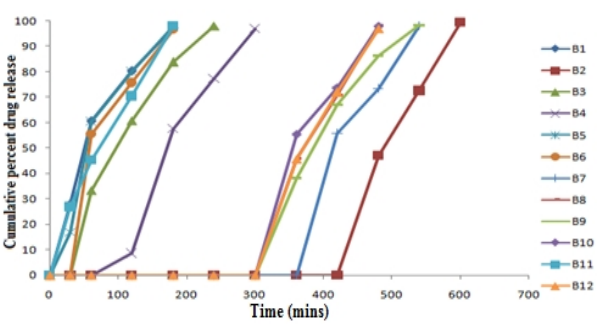


Figure 3 and Figure 4: *In-vitro* dissolution profiles of press-coated tablet formulations

RESULTS

The RRCT4 batch made up of 10% psyllium seed mucilage was selected as the best core tablet showing disintegration time of 30±1.73 sec, wetting time of 49.6±3.21 sec and Cumulative % drug release of 99.09% at the end of 3 hrs.

The press-coated tablets were formulated by both direct compression method and wet granulation method and were evaluated for thickness, hardness, average weight, friability, *in-vitro* release and rupture test. *In-vitro* release profiles of pulsatile device during 10 h studies were found to have very good sustaining efficacy.

All the formulations showed distinct lag time. Formulation A1, A8, B2 and B7 were selected as the best formulations with formulation B2 prepared by wet granulation method containing xanthan gum and dammar gum in the ratio 2:1 having maximum lag time of 7 h 15 min, highest swelling index of 89.44% and Cumulative % drug release of 99.29% at the end of 10 h of study.

The stability studies were carried out for the selected formulations (A1, A8, B2 and B7) at 40±2°C/ 75±%5 RH for one month. The results indicated that the tablets did not show any physical changes (hardness and friability) during the study period and the drug content was found above 97% at the end of one month. This indicates that tablets are fairly stable at storage condition.

DISCUSSION

From the present study it could be concluded that natural superdisintegrant like psyllium seed mucilage is suitable candidate for formulation of RRCT. The lag time for all the formulations was directly proportional to the concentration of XG or GG. Increase in the amount of XG or DG increased the lag time, because it swells to a very large extent, and form pores and dissolution of the external coat was at a very slow rate. Increase in amount of DG and chitosan decreased the lag time, because DG has sticking/adhering property when it comes in contact with water along with matrix forming property and chitosan which undergoes swelling at pH 6.8 and above. Combination of the properties of both hydrophilic and hydrophobic polymers were responsible for the lag time. Increase in lag time of press-coated pulsatile tablets formulated by wet granulation method as compared to the direct compression method because 5% PVP K90 was used as granulating agent which has hydrating property when it comes in contact with water.

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