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DESIGN, DEVELOPMENT AND EVALUATION OF CHRONOTHERAPEUTIC TABLETS CONTAINING BOSWELLIA SERRATA AND GINGER OFFICIANALES IN THE TREATMENT OF ARTHRITIS

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Abstract:
The objective of the present research was to formulate a chronotherapeutic oral delivery system for the treatment of Rheumatoid Arthritis. The active ingredients were a combination of Boswellia serrata & ginger extracts. To achieve a chronotherapeutic system many polymers were used as retardants. Formulation of uncoated tablets was done by direct compression method. Powder blends were evaluated for precompression parameters like bulk density, tapped density, Hasuner's Ratio, % CI and angle of repose.The results showed that the powder blends exhibited good flow properties. In this method, Superdisintegrants like cross PVP were used in concentrations (4-11%w/w), sodium starch glycolate were used in concentrations (8-10%w/w) and disintegrant starch was used in combination with cross PVP in 7.5%w/w concentration each. Optimization was done by varying the disintegrant concentrations. Various post compression parameters like hardness, thickness, weight variation, friability, disintegration time and in-vitro dissolution studies were checked for optimizing the formulation. Batches showing disintegration of less than 30 mins were taken further for coating experiments. Formulation of coated tablets for chronotherapeutic release were done by different polymer coatings to achieve chronotherapeutic release. Eudragit S-100 coat was optimized as it provided a better lag time than other formulations. Characterization and Evaluation of coated tablets: Chronotherapeutic tablets of Boswellia serrata and ginger were formulated and batch ET2 was optimized which showed percent drug release 82.32% of Boswellia serrata and 98.98% of ginger at the end of 12 hours.

Key words: *Chronotherapeutic delivery, Boswellia serrata, ginger and Eudragit S-100*

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INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that can affect more than just your joints. The stiffness seen in active RA is most often worst in the morning. A broad range of drugs are prescribed for managing the pain and slowing the progression of RA. Doctors often prescribe DMARDs along with non-steroidal anti-inflammatory drugs or NSAID's, to lower swelling, pain and fever. The only side effects of NSAID's on long term usage are gastro intestinal disturbances and peptic ulceration.

Natural products from plants have played a remarkable role to cure and avert different diseases from ancient times. Herbal supplements of Boswellia serrata, Curcuma longa, Aloe vera, Ginger, Fish oil, Withania somnifera have been used for treatment of arthritis. Boswellia extracts rich in the boswellic acid inhibit inflammation by blocking TNF-alpha and mediators. Ginger extracts consists of the active constituents 6-shoagaol and 10- Gingerol showed the most anti-inflammatory activity. A combination of these two extracts can be used for synergistic activity for arthritis.

Rheumatoid arthritis exhibits diurnal variation in symptoms, with patients suffering with increased painful joint stiffness in the early morning. This correlates with an early morning rise in circulating levels of pro-inflammatory cytokines, such as interleukin-6. That is why for diseases based on circadian rhythms, chronotherapeutic drug delivery systems are used. It is mainly concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The specific time that patients take their medication is very important as it has significant impact on treatment success.

A chronotherapeutic tablet formulation containing Boswellia serrata extracts and Ginger extracts were developed. This combination was used to achieve synergistic effects. The core tablets were prepared by using different superdisintegrants like Cross PVP and Sodium starch glycolate. The core tablet was then coated using a variety of enteric coated polymers like Eudragit S-100 and Cellulose acetate phthalate. These coats remain intact in stomach, and dissolve in small intestine providing the essential lag time and allowing the drug to release when it is actually needed, thereby achieving the chronotherapy for RA.

MATERIALS AND METHODS:

Materials:

Boswellia serrata, Ginger and Aloe Vera was obtained as a gift sample from Konark Herbals Pvt Ltd. Avicel pH 102 was obtained from FMC Biopolymer. Eudragit S100 from Evonik India. Cross PVP and Talc was procured from BASF. Rest all excipients and chemicals used were of analytical (AR) grade and purchased from SD Fine-chem Ltd., Mumbai.

Methods:

Development of uncoated core tablet form by Wet granulation method

The core tablets were prepared by wet granulation method which consisted of 250 mg of Boswellia serrata and 250 mg of Ginger as the active ingredients. The herbal extracts, diluent Avicel pH 102, superdisintegrant cross PVP (5%) and binder aloe vera were weighed and sieved through 40# and mixed uniformly. The solvent IPA was added drop wise till a wet mass was formed. The wet mass was passed through 12# and the granules obtained were dried at 60°. The dried granules were then passed through 22#. Talc and magnesium stearate were sieved through 60# and then added to the granules.[1]

Table 1: Formulation batch of F1 for the core uncoated tablets

Ingredients	F1
Boswellia serrata	250 mg
Ginger	250 mg
Cross PVP (5%)	30mg
Avicel pH 102	3 mg
Aloe vera (1%)	3 mg
Talc (0.5%)	58 mg
Mg stearate (0.5%)	6 mg
Isopropyl alcohol	q.s
Tablet weight	600 mg

Development of uncoated core tablet form by Dry granulation method

The core tablets were formulated by direct compression method which consisted of 250 mg of Boswellia serrata and 250 mg of Ginger as the active ingredients. Superdisintegrants like cross PVP were used in concentrations (4-11%w/w), sodium starch glycolate were used in concentrations (8-10%w/w) and disintegrant starch was used in combination with cross PVP in 7.5%w/w concentration each. The herbal extracts, diluent Avicel pH 102, Aloe vera and superdisintegrant were passed through 40# and blended together for 5 minutes. The lubricant magnesium stearate and glidant talc were passed through 60# and blended with the above mixture. The mixed blend of excipients was compressed into tablets on a single punch compression machine. The punch size for batches F2 and F3 was 11.9 mm and it was changed to 21x9 mm for batches F5-F11 which gave capsule shaped tablets. The punch size for batch F14 was changed to 18.4x 9 mm. The punches used were standard concave punches which proved to be suitable for coating. The ingredients used to prepare the different formulation batches are shown in table 2 and table 3. [2]

Table 2: Formulation batches from F2-F8 for the core uncoated tablets

INGREDIENTS	F2	F3	F4	F5	F6	F7	F8
Boswellia serrata	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Ginger	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Cross PVP	24 mg	28 mg	32 mg	40 mg	56 mg	72 mg	80 mg
Sodium starch glycolate	-	-	-	-	-	-	-
Starch	-	-	-	-	-	-	-
Aloe vera	-	3.5 mg	4 mg	4 mg	4 mg	4 mg	3.5 mg
Avicel	67 mg	158 mg	248 mg	240 mg	224 mg	208 mg	200 mg
Talc	6 mg	7 mg	8 mg	8 mg	8 mg	8 mg	8 mg
Mg stearate	3 mg	3.5 mg	8 mg	8 mg	8 mg	8 mg	8 mg
Tablet weight	**600 mg**	**700 mg**	**800 mg**	**800 mg**	**800 mg**	**800 mg**	**800 mg**

In batches F2-F8 the disintegrant used was Cross PVP. A concentration of 4% to 10% disintegrant was used.

Table 3: Formulation batches from F9-F14 for the core uncoated tablets

INGREDIENTS	F9	F10	F11	F12	F13	F14
Boswellia serrata	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Ginger	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Cross PVP	-	-	-	88 mg	60 mg	60 mg
Sodium starch glycolate	64 mg	72 mg	80 mg	-	-	-
Starch	-	-	-	-	60 mg	60 mg
Aloe vera	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
Avicel	216 mg	208 mg	200 mg	192 mg	110 mg	110 mg
Talc	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg
Mg stearate	8 mg	8 mg	8 mg	8 mg	8 mg	8 mg
Tablet weight	**800 mg**	**800 mg**	**800 mg**	**750 mg**	**750 mg**	**750 mg**

In batches F9-F11 the disintegrant used was sodium starch glycolate in the concentration of 8-10%. A combination of Cross PVP and starch were used in the ratio of 1:1 in the concentration of 15% in batches F13 and F14.

Evaluation of Pre-compression parameters of uncoated tablets

The prepared powder blend were evaluated for pre compression parameters like Angle of repose, bulk density, tap density, compressibility index and Hausner's ratio.

Evaluation of Post compression parameters of uncoated tablets

The prepared powder blend were evaluated for post compression parameters like Hardness, Weight Variation, friability, tablet dimensions, *In-vitro* disintegration and *In-vitro* Dissolution studies.

a.) In-vitro Disintegration time: The disintegration time of tablet was determined using disintegration apparatus in pH 6.8 buffer as disintegration medium maintained at 37˚C ±2˚C. When all the six tablets are completely disintegrated, the time was noted. [3]

b.) In-vitro Dissolution studies: Dissolution studies were conducted to determine the release pattern of the drug from the product. Dissolution test for the uncoated tablet was carried out as per USP method for dissolution test for tablets using apparatus II (paddle type). Dissolution medium used was 900 mL of 6.8 pH phosphate buffer with 1.5% SLS, agitation speed at 100 rpm at 37±0.5 ˚C. An aliquot sample of 5 mL was withdrawn at different time periods and replaced with fresh medium to maintain sink conditions. Samples were taken at interval of 5, 10, 15, 30, 45, 60 and 120 minutes, filtered and diluted suitably. Absorbance of the resulting solution was measured at 244 and 277 nm.[4]

Formulation Development of Oral Coated tablet

Selection of Coating material

The optimized core tablet formulation of Boswellia serrata and Ginger were coated with different enteric coated polymers like Eudragit S-100, hydroxy propyl methyl cellulose phthalate (HPMCP) and different ready mix like Instacoat En-Sol and Dr Coat-ECS (cellulose acetate phthalate). Coating was done on a conventional pan coating system (R & D coater). Different levels of coating of the polymeric layers are shown in table 4. The compositions of coating solutions are given in table 5, 6, 7 and 8.The conditions of coating operation are given in table 9.

Table 4. Different levels of polymer coatings

Batch No	C1	C2	C3	C4	C5
Polymers	Instacoat En-sol	Dr Coat-ECS	NOVOMIX-Ent	Eudragit S-100 with Dibutyl phthalate	Eudragit S-100 with tri ethyl citrate
Type	Organic				
Percent Concentration	2%	5%	5%	3%	3-5%
Percent Weight Gain	-	15, 20, 25 and 30%	-	10,15,20,25 and 30%	5-45%

Batch C4 and C5 were prepared by the polymer Eudragit S-100 with different plasticizers. Batch C2 was a ready mix and was done by organic coating with a weight gain from 15-30%. In batches C1 and C3 coating was not done due to settling of the coating solution.

Optimizing the final coating solutions

The conditions of coating operation are given below.

Table 5. Compositions of coating solution of Eudragit S-100 with Dibutyl phthalate and tri ethyl citrate

INGREDIENTS	QUANTITY
Eudragit S-100	96%
Dibutyl phthalate	3%
Talc	1%
Ethanol	100 ml

INGREDIENTS	QUANTITY
Eudragit S-100	95%
Tri ethyl citrate	5%
Talc	1%
Ethanol	100 ml

Eudragit S-100 coating solution was prepared by dissolving Eudragit S-100 in 100 ml of ethanol and stirred for one hour. Plasticizer and anti-tacking agent talc was added and further stirred for 15-20 minutes.

Table 6. Compositions of coating solution of Dr Coat-ECS

INGREDIENTS	QUANTITY
Dr Coat- ECS	5%
Titanium Dioxide	1%
Ethanol	100 ml

Coating solution of Dr Coat-ECS was prepared by dissolving the ready mix in 100 ml of ethanol and stirred for 45 minutes. Titanium dioxide was added as the opacifier and then continued to stir for further 45 minutes.

Table 7. Compositions of coating solution of Instacoat En-sol

NGREDIENTS	QUANTITY
Instacoat En-sol	2 %
IPA	35%
Acetone	65%

Instacoat En-sol coating was prepared by dissolving the polymer in 35% IPA and stirring it for 15 minutes. 65% acetone was then added to this solution and continuously stirred for 45 minutes.

Table 8. Compositions of coating solution of NOVOMIX-ENT

INGREDIENTS	QUANTITY
NOVOMIX-ENT	5%
Talc	1%
IPA	100 ml

dissolving the ready mix in 100 ml of IPA and stirred for 45 minutes. The opacifier talc was added slowly and the solution was stirred continuously for one hour.

Table 9. Coating Parameters for Organic Coat

Parameters	Organic coating
Pan diameter	4”
Pan speed	23-35 rpm
Baffles	3
Inlet temperature	55-60 °C
Spray nozzle	0.7 mm
Pump speed	1 rpm

The inlet temperature of the pan was maintained about 55-60 °C to ensure proper drying of the tablets. Pump speed was also kept at 1 rpm so that coating solution was sprayed evenly.

Evaluation of Post-Compression Parameters of Coated Tablets

a.) Hardness, friability, weight variation and tablet dimensions

The hardness of the coated tablets were measured by Monsanto hardness tester, friability was measured by Roche friabilator and weight variation was done by measuring 20 tablets and taking the average weight. The tablet dimensions were checked by a calibrated vernier caliper. [5,6,7]

b.) Lag time of coated drug delivery systems (Rupture test)

The time at which the outer coating layer starts to rupture is defined as the lag time. The intention of the study was to develop enteric coated tablets which remain protected from gastric environment and will release the drug rapidly in the intestine after administration. Providing suitable lag time for the enteric coated tablets would serve the purpose. Hence Lag time was determined, by placing the coated tablets in USP dissolution apparatus II containing 900 ml of 0.1 N HCl for initial 2 hours and then changing to phosphate buffer of pH 6.8 till the coating ruptures. The media was agitated at 100 rpm and maintained at 37±0.5°C.[8]

c.) In-vitro Drug Evaluation of coated tablet

Dissolution studies of the enteric coated tablets were carried out in triplicate, employing USP type-II apparatus following conditions that simulate gastrointestinal tract. 0.1N HCl with 1.5% SLS and phosphate buffer of pH 6.8 with 1.5% SLS were used as dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5^{0}C with a stirring speed of 100 rpm. Initially tablets were subjected to dissolution in 0.1N HCl with 1.5% SLS for 2 hours and after that the media was changed to phosphate buffer pH 6.8 with 1.5% SLS. Samples were taken at intervals of every hour and analysed for percent drug release at 245 and 277 nm. A dissolution study was carried out for 12 hours and the drug release was determined.[9]

Stability Studies

Stability studies were carried out on the optimized formulations to determine the effect of various excipients on the stability of the drug. Optimized formulations were kept for stability studies at and for two months. The samples were kept at the following conditions as per ICH guidelines.

a) 25±2˚C / 65±5% RH
b) 40± 2˚C / 75±5% RH

The samples were withdrawn and evaluated for the following parameters [10]

a) General appearance
b) Drug content
c) In-vitro lag time
d) In-vitro release

RESULT AND DISCUSSION:

Development of uncoated core dosage form by wet granulation

In **batch F1** the granules which were obtained by wet sieving were too sticky and it took a lot of time to dry. The resultant granules were too hard and

could not be compressed. Also it was found that Boswellia serrata being a resin possessed binding properties and it showed incompatibilities with other solvents. Due to this, the method of wet granulation was avoided and the next batches were done by direct compression.

Development of uncoated core dosage form by direct compression

In **batch F2** the ingredients were properly blended and compressed in tablets using 11.9 mm punch. The hardness of the tablets was kept at 6 kg/cm^2. The disintegrants used was 4% of cross PVP and the tablet weight was 600 mg. The tablets compressed showed signs of picking to the upper punch. To minimise the picking of tablets diluents were added in the next batch. In **batch F3** the ingredients were blended together and compressed in tablets using round capsule shaped 18.4x9 mm punch keeping the hardness at 6 kg/cm^2 and 4% disintegrants. The tablet weight was increased to 700 mg. The tablets still showed picking to the upper punch. For further optimisation of the batch more amount of diluent was added in batch F4. **Batch F4** the ingredients were blended and compressed using round capsular shaped 21x9 mm punch. Due to the increase in amount of diluent the punch size was changed. The tablet hardness was changed to 5 kg/cm^2 and disintegrants remained the same and the weight of the tablet was made to 800 mg. No picking was observed in this batch. The disintegration time of batch F4 was 54 minutes which did not meet the requirements of USP. The concentration of disintegrants was increased in the next batch. In **batches F5-F8** the disintegrants cross PVP was increased to from 5% to 10% and the hardness was maintained at 5 kg/cm^2. The disintegration time of the tablets were checked. Batch F8 which consisted of 10% cross PVP showed a disintegration time of 13 minutes. Cross PVP in higher concentration showed better disintegration. A new disintegrants was tried in the next batch. **Batches F9-F11** were prepared with varying concentrations of the disintegrants sodium starch glycolate from 8% to 10% and the hardness in batch F9 and F10 was reduced to 4.5 kg/cm^2. Batch F11 showed a disintegration time of 14 minutes. This showed that sodium starch glycolate did not provide better disintegration time than cross PVP. In **batch F12** cross PVP was used again with 11% concentration keeping the hardness 5 kg/cm^2 and the tablet weight was reduced to 750 mg. This greatly reduced the disintegration time to 7 minutes. The disintegration time further was checked by using a combination of disintegrants in the next batch. **Batch F13** was formulated using a combination of disintegrants like 7.5% starch and 7.5% cross PVP. The hardness was maintained at 5 kg/cm^2 and. The combination of disintegrants caused the disintegration time to change to 2 minutes. However the density of starch was more and so the tablets formed became more compact and the thickness of the tablet changed. To solve this **batch F14** was formulated in which the punch size was changed to 18.4x9 mm. The disintegration time was found out to be 4 minutes.

Pre-compression parameters of the core uncoated tablet

The powder blend of all the batches were subjected to many Precompression parameters like angle of repose, bulk density and tap density. Table 10 and 11 showed the evaluation results of Pre compression parameters of the powder blends.

Table 10. Pre-compression parameters of Batches F2- F8 of uncoated tablets

Parameters	F2	F3	F4	F5	F6	F7	F8
Angle of repose (°)	37.54	35.90	32.74	30.32	31.45	29.14	29.78
Bulk density (gm/ml)	0.33	0.33	0.30	0.30	0.28	0.28	0.28
Tapped density (gm/ml)	0.57	0.57	0.44	0.44	0.40	0.40	0.40
Carr's index (%)	35.23	35.98	31.74	28.63	25.12	23.98	23.12
Hausner's ratio	1.43	1.40	1.38	1.37	1.37	1.30	1.30

Table 11. Pre-compression parameters of Batches F9-F14 of uncoated tablets

Parameters	F9	F10	F11	F12	F13	F14
Angle of repose (°)	27.81	27.12	27.49	29.91	28.31	28.68
Bulk density (gm/ml)	0.38	0.39	0.41	0.35	0.38	0.38
Tapped density (gm/ml)	0.61	0.63	0.65	0.58	0.54	0.54
Carr's index (%)	19.12	19.04	18.12	22.89	19.51	19.56
Hausner's ratio	1.20	1.20	1.19	1.29	1.24	1.24

From the above tables it was observed that the flow properties of **Batch F9, F10, F11 and F12** were good according to the requirements in IP. The batches in which Sodium starch glycolate was used as a disintegrant the flow properties were better as compared to Cross PVP and starch.

Post-compression parameters of the core uncoated tablets

The different batches of the core tablets were subjected to various evaluation tests for hardness, weight variation, friability, disintegration time, drug content and in-vitro dissolution studies. Table 14 and 15 show the evaluation results of Post compression parameters of the core tablets.

Batches F4 and F5 showed best percent friability of 0%. All the batches passed the percent friability which is less than 1%. The disintegration time of **Batches F11, F12, F13 and F14** showed disintegration time below 15 minutes which passes according to USP, results were shown in tables 12 and 13.

***In-vitro* dissolution studies of the core uncoated tablet**

Dissolution medium taken was 1.5% SLS in phosphate buffer pH 6.8 as the core tablet releases in the small intestine. The temperature was maintained at 37±0.5˚C with an agitation speed of 100 rpm.

Table 12. Post-compression parameters of Batches F2-F8 of uncoated tablets

Parameters	F2	F3	F4	F5	F6	F7	F8
Hardness (kg/cm^2)	6	6	5	5	5	5	5
Thickness (mm)	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Friability (%)	0.3	0.3	0	0	0.8	0.5	0.6
Weight variation	600±0.07	700±0.02	800±0.05	800±0.04	800±0.07	800±0.06	800±0.02
Disintegration time (minutes)	72	68	53	32	20	15	13

Table 13. Post-compression parameters of Batches F9-F14 of uncoated tablets

Parameters	F9	F10	F11	F12	F13	F14
Hardness (kg/cm^2)	4.5	4.5	5	5	5	5
Thickness (mm)	5.5	5.5	5.5	5.5	5.5	5.5
Friability (%)	0.3	0.3	0.4	0.5	0.5	0.4
Weight variation	800±0.02	800±0.03	800±0.04	750±0.04	750±0.02	750±0.02
Disintegration time (minutes)	25	19	12	7	2	4
Drug Content (Percent)	98	99	98	101	101	99

Table 14. *In- vitro* dissolution profile Boswellia serrata in phosphate buffer 6.8+1.5% SLS in uncoated tablet

Time (mins)	F5	F6	F8	F9	F11	F12	F13	F14
5	15.32	20.68	27.68	20.13	20.52	27.61	22.74	24.41
10	7.78	7.14	24.98	9.45	9.89	12.00	28.75	27.32
15	9.09	12.32	29.51	11.28	12.12	14.89	44.03	38.57
30	16.25	19.24	37.54	17.62	29.98	40.04	81.29	82.36
45	23.21	25.21	46.12	24.98	32.45	54.22	89.36	89.14
60	26.37	31.25	53.24	29.75	39.17	70.05	95.15	96.42
120	29.12	38.65	63.32	35.75	43.2	71.73	108.3	110

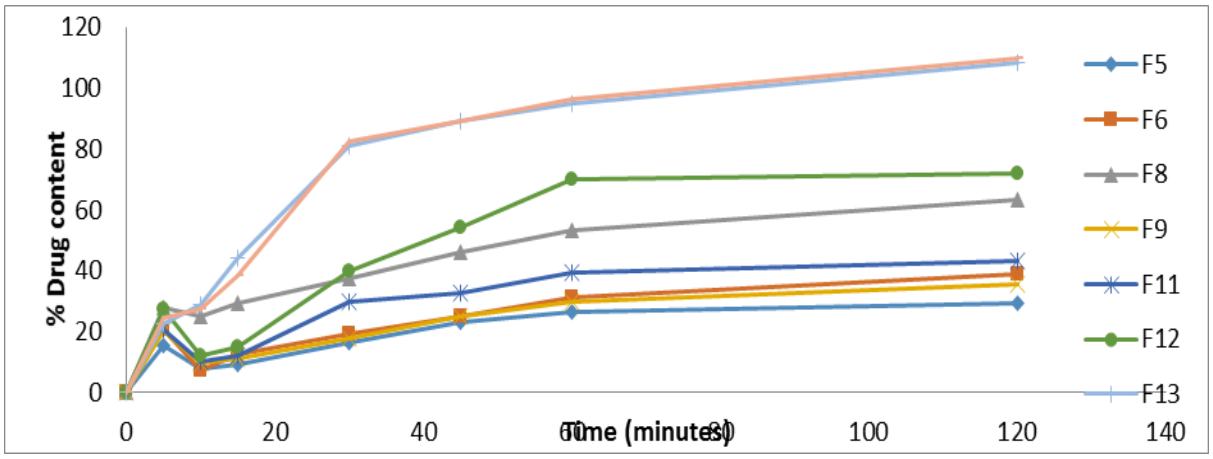

Figure 1. Percent drug release of Boswellia serrata for uncoated tablets

The rate of drug release for Boswellia serrata for batch F13 in 30 minutes was 81.29% and for batch F14 was 82.36% which was met under the requirements of USP. Batch F13 and F14 had a combination of disintegrants of cross PVP and starch in the ratio of 1:1.

Table 15. *In- vitro* dissolution profile Boswellia serrata in phosphate buffer 6.8+1.5% SLS in uncoated tablet

Time (mins)	F5	F6	F8	F9	F11	F12	F13	F14
5	19.32	27.12	29.74	26.12	21.98	23.80	67.91	32.48
10	15.32	20.41	25.98	24.32	17.63	19.00	69.63	52.27
15	23.12	23.01	29.12	38.10	29.41	28.08	83.84	79.90
30	29.41	28.12	37.84	41.41	42.15	53.53	91.12	86.17
45	34.31	36.78	43.74	49.10	49.32	71.81	95.21	90.87
60	40.31	51.32	64.32	63.12	57.21	80.30	104.21	98.31
120	36.10	54.12	73.98	59.31	69.74	107.48	109.45	110.98

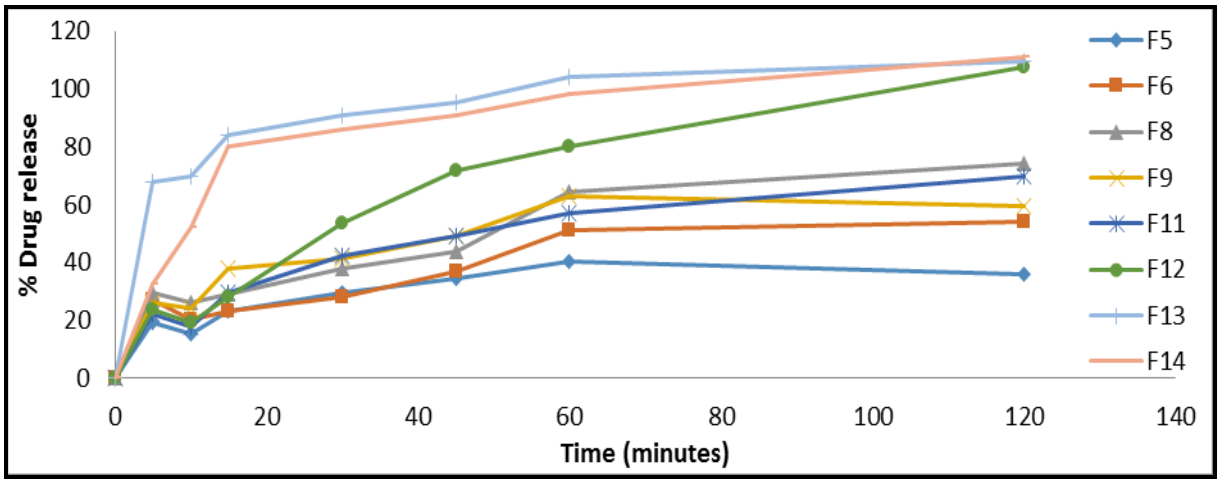

Figure 2. Percent drug release of Ginger for uncoated tablets

The rate of drug release for Ginger for batch F13 in 30 minutes was 91.12% and for batch F14 was 86.17% which was met under the requirements of USP. In this way **batch F14** was optimised as the core uncoated tablets and the post compression parameters were checked.

Development and evaluation of coated oral dosage form

Coating with Instacoat En-sol:

Batch C1 was prepared with ready mix Instacoat En-sol (2%w/w). The coating batch failed since the solution formed started settling during coating and only the solvent was being sprayed. Dissolution studies could not be carried out.

Coating with Dr Coat- ECS:

Batch C2 coating was done by ready mix Dr Coat-ECS (5%w/w). Coating formed was uniform and a weight gain from 15-30% was done. Dissolution studies were further carried out.

Table 16. In-vitro dissolution profile of Boswellia serrata with different polymeric coatings of Dr Coat-ECS

Time (hours)	D1 (15% coat)	D2 (20% Coat)	D3 (25% Coat)	D4 (30% Coat)
1	0.01	0.01	0.01	0.01
2	0.09	0.04	0.02	0.01
3	83.51	79.32	71.01	63.51
4	91.45	87.12	78.14	79.12
5	101.9	98.12	91.74	89.41

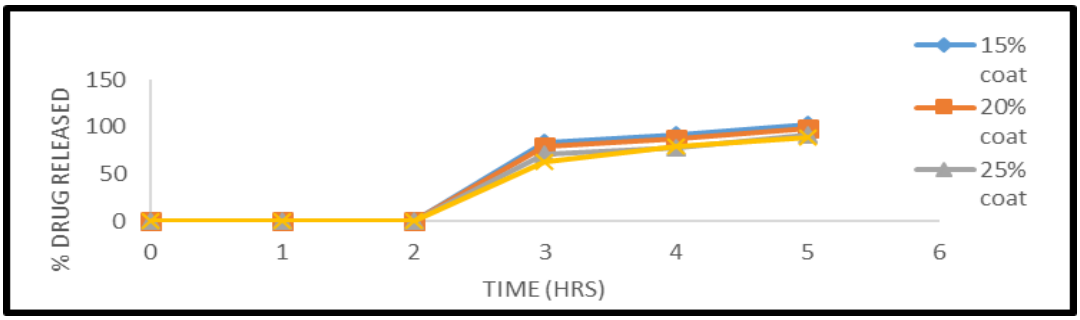

Figure 3. Percent drug release of Boswellia serrata with coating of Dr Coat-ECS

Table 17. In-vitro dissolution profile of Ginger with different polymeric coatings of Dr Coat-ECS

time (hours)	D1 (15% coat)	D2 (20% Coat)	D3 (25% Coat)	D4 (30% Coat)
1	0.01	0.01	0.01	0.01
2	0.09	0.04	0.02	0.01
3	79.21	69.12	63.21	51.02
4	84.21	75.98	69.59	62.38
5	92.78	82.31	76.12	69.99

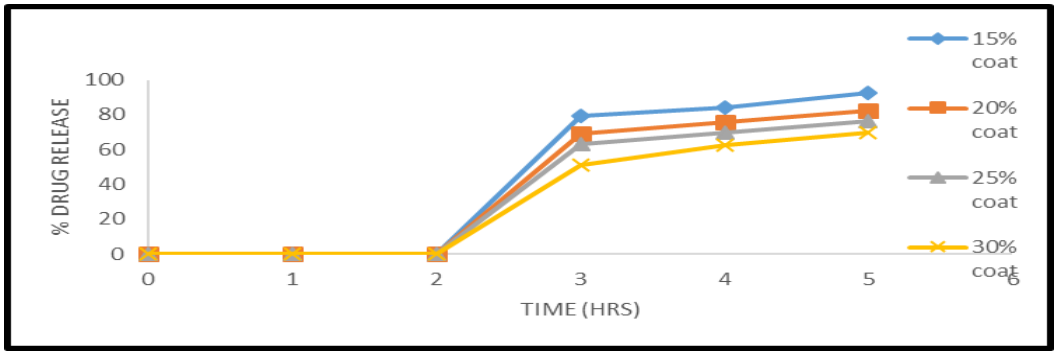

Figure no 4. Percent drug release of Ginger with coating of Dr Coat-ECS

Batch C2 coating with Dr Coat-ECS showed a lag time of only 2 hours and more than 50% drug was released by the end of 3 hours in the case of batch D4. Hence other polymer coatings were tried.

Coating with NOVOMIX-ENT

Batch C3 coating was prepared with ready mix Novomix-ENT (5%w/w). The batch failed because coating on the tablet was not formed. Also the coating solution started settling and only the solvent was being sprayed. Dissolution studies could not be carried out.

Coating with Eudragit S-100 with Dibutyl Phthalate (DBP) as the plasticizer

Batch C4 coating was prepared with Eudragit S-100 with dibutyl phthalate as the plasticizer. A weight gain of 10-30% was done. The coating formed was uniform and the tablet surface was smooth. Dissolution studies were further carried out.

Table 18. In-vitro dissolution profile of Boswellia serrata with different polymeric coatings of Eudragit S-100+ DBP

time (hours)	ED1 (10% coat)	ED2 (15% coat)	ED3 (20% coat)	ED4 (25% coat)	ED5 (30% coat)
1	0.01	0.001	0.001	0.001	0.001
2	0.02	0.02	0.01	0.01	0.01
3	79.21	65.12	58.75	49.21	53.12
4	81.23	72.36	67.21	59.74	61.25
5	99.12	79.24	72.24	65.1	68.9
6	100.78	89.36	81.25	72.66	72.6
7	102.3	98.31	89.12	82.54	79.32

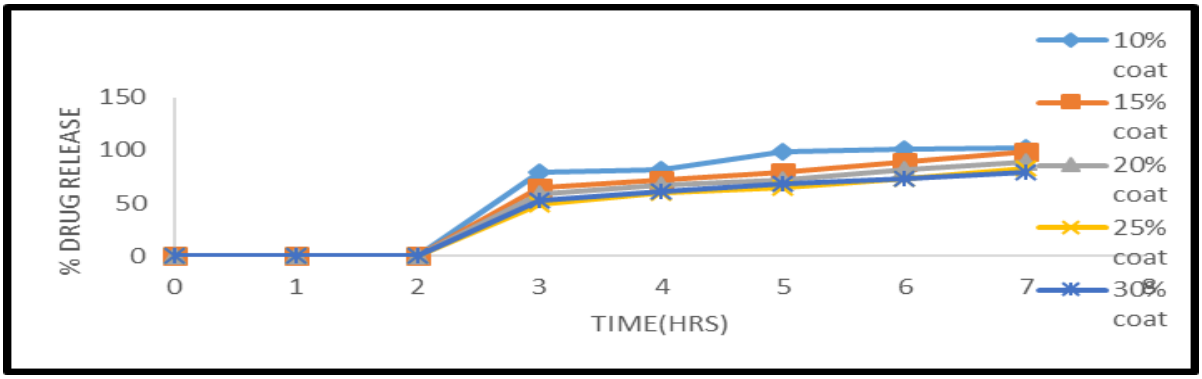

Figure 5. Percent drug release of Boswellia serrata with coating of Eudragit S-100+DBP

Table 19. In-vitro dissolution profile of Ginger with different polymeric coatings of Eudragit S-100+ DBP

time (hours)	ED1 (10% coat)	ED2 (15% coat)	ED3 (20% coat)	ED4 (25% coat)	ED5 (30% coat)
1	0.01	0.001	0.001	0.001	0.001
2	0.08	0.05	0.01	0.01	0.01
3	75.12	61.24	58.21	49.21	35.21
4	85.36	68.95	63.25	59.74	45.95
5	98.65	75.32	69.12	65.1	51.21
6	99.28	83.95	80.21	72.66	59.21
7	101.6	97.12	84.36	82.54	68.21

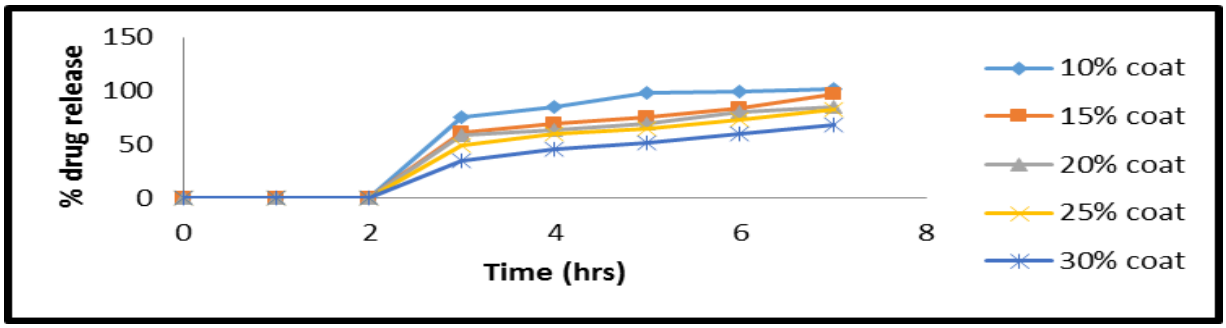

Figure 6. Percent drug release of Ginger with coating of Eudragit S-100+DBP

Batch C4 coating with Eudragit S-100with dibutyl phthalate showed a lag time of only 2 hours and more than 50% drug was released by the end of 3 hours in the case of batch ED4. Hence other polymer coatings were tried.

Batch C5 coating was done with Eudragit S-100 with a hydrophobic plasticizer as tri ethyl citrate. A weight gain from 5-45% was done. The coating formed was uniform and tablet surface was smooth. Dissolution studies were further carried out.

Coating with Eudragit S-100 and Tri ethyl citrate as the plasticizer

Table 20. In-vitro dissolution profile of Boswellia serrata with different polymeric coatings of Eudragit S-100+ TEC

Time (hours)	ET1 (5% coat)	ET2 (10% coat)	ET3 (15% coat)	ET4 (20% coat)
1	0.05	0.001	0.001	0.001
2	0.09	0.01	0.012	0.011
3	5.600	0.39	0.48	0.48
4	25.54	0.50	1.67	0.69
5	53.17	10.07	6.17	0.50
6	56.77	13.63	14.05	2.32
7	73.17	22.23	15.76	3.97
8	87.21	26.90	28.53	9.33
9	99.41	37.01	29.98	11.99

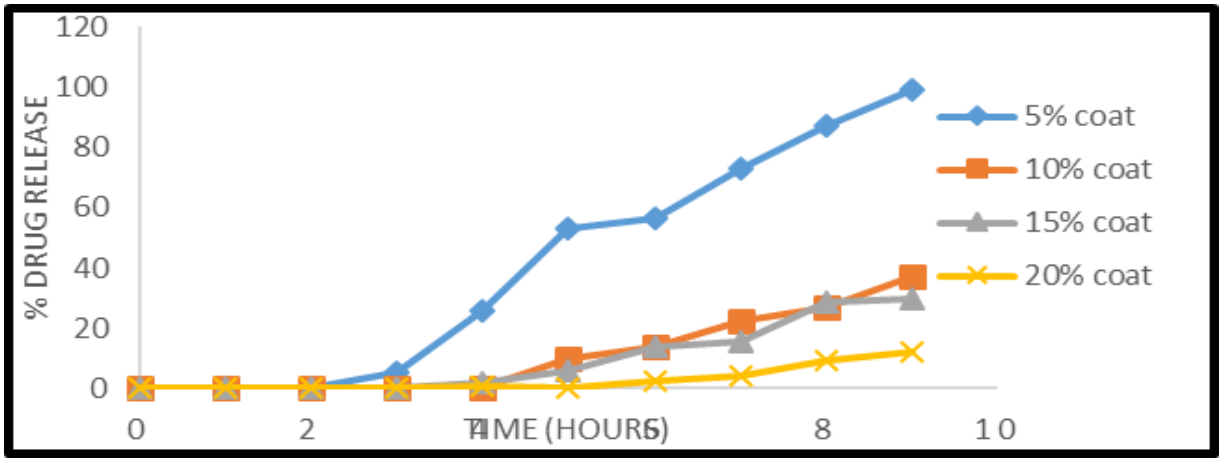

Figure 7. Percent drug release of Boswellia serrata with coating of Eudragit S-100+TEC

Table 21. In-vitro dissolution profile of Ginger extract with different polymeric coatings of Eudragit S-100+ TEC

Time (hours)	ET1 (5% coat)	ET2 (10% coat)	ET3 (15% coat)	ET4 (20% coat)
1	0.05	0.0021	0.001	0.001
2	0.21	0.064	0.12	0.011
3	14.31	1.73	0.38	0.38
4	50.76	2.18	2.26	2.18
5	69.29	16.19	6.69	3.033
6	73.14	20.62	19.95	3.41
7	81.32	31.87	22.96	7.18
8	82.67	40.09	41.40	17.89
9	95.36	54.35	45.56	20.12

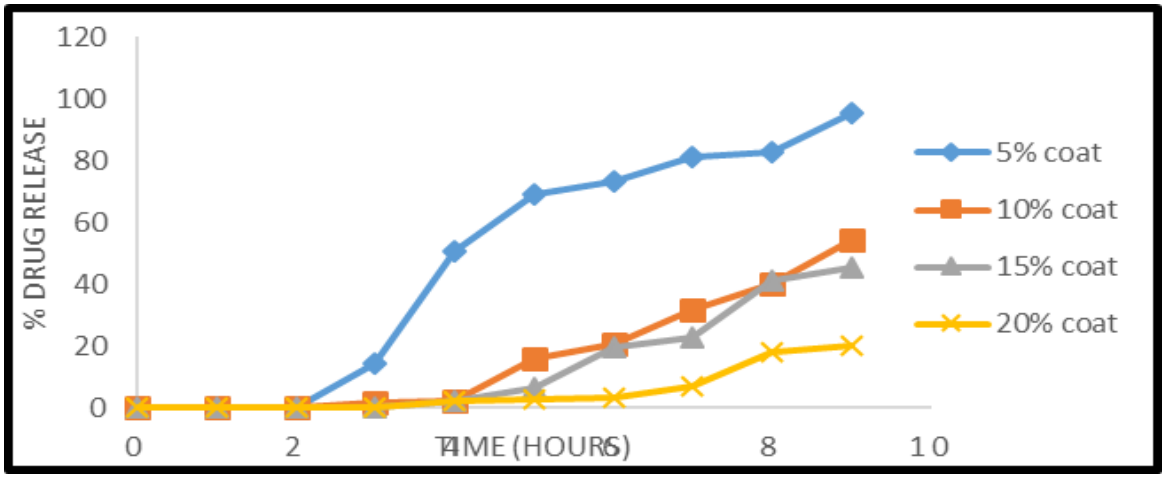

Table 8. Percent drug release of Ginger with coating of Eudragit S-100+TEC

Dissolution of the coated tablets was first done in 0.1N HCl for initial 2 hours. The tablets did not disintegrate in 0.1 N HCl. The medium was then changed and replaced by 1.5% SLS in Phosphate buffer pH 6.8. The dissolution was carried out for 9 hours. The coating of the tablet started eroding when the tablet came in contact with pH 6.8 phosphate buffer because Eudragit S-100 is a pH dependent polymer and it starts dissolving above pH 6.8. The lag time was also more than 3 hours.

Post Compression Parameters of Coated Tablets

Hardness, Friability and weight variation

Different batches of the enteric coated tablets were subjected to various evaluation tests for hardness, weight variation, friability, lag time and invitro dissolution studies. Table 22 show the evaluation results of Post compression parameters of the enteric coated tablets.

Table 22. Post Compression parameters of coated tablets

	C2	C4	C5
Hardness (kg/cm^2)	7±0.0	7±0.1	7±0.11
Friability (%)	0	0	0
Weight variation	750 ±0.06	750±0.05	750±0.05
Thickness (mm)	6	6	6

Lag time of core coated tablets

The lag time of all the batches were carried out and it was found out that **batch C4** and **batch C5** showed a lag time of more than 3 hours.

***In-vitro* Dissolution studies of coated tablet for 12 hours**

In-vitro dissolution studies of the optimised coated tablet of Eudragit S-100+TEC was continued till 12 hours in order to check the chronotherapeutic release of the tablet. 10% coat (ET2) batch was optimised and dissolution was checked till 12 hours.

Table 23. Percent drug release of Boswellia serrata and Ginger in 12 hours with coating of Eudragit S-100+TEC

Time (hours)	Boswellia serrata	Ginger
1	0.0021	0.0021
2	0.0123	0.064
3	0.39	1.73
4	0.5	2.181
5	10.07	16.19
6	13.63	20.62
7	22.238	31.87
8	26.9	40.09
9	37.019	54.353
10	51.65	71.2158
11	69.98	86.221
12	82.32	98.985

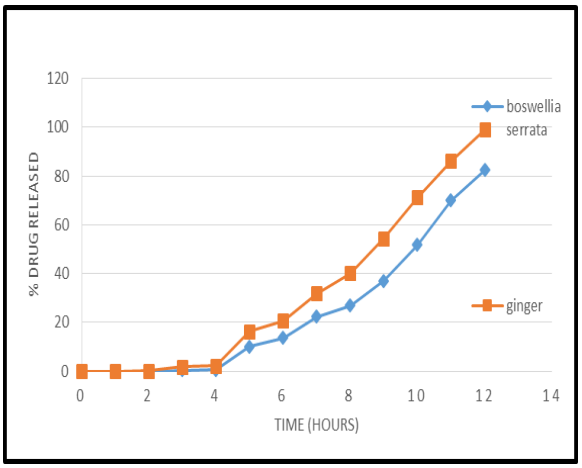

Figure 9. Percent drug release of Boswellia serrata and Ginger with Eudragit S-100+TEC

Chronotherapeutic tablets of Boswellia serrata and Ginger were formulated and batch ET2 was optimized which showed percent drug release 82.32% of Boswellia serrata and 98.98% of Ginger at the end of 12 hours.

Stability studies

The parameters related to stability of the formulation were found to be within limits at the end of two months. The physicochemical properties of the formulation did not show any change over two months of storage at different temperature and humidity conditions.

Table 24. Two month stability data at 25±2°C and 60±5% RH

Tests	Specification	Initial	1 Month	2 Month
Description	Yellowish brown coloured caplet	Yellowish brown coloured caplet	Yellowish brown coloured caplet	Yellowish brown coloured caplet
Weight (mg)	825±5% mg	825-827	827-828	827-828
Thickness (mm)	-	6	6	6
Hardness (kg/cm^2)	-	5	5	6
Assay (%) [Boswellia serrata & Ginger]	-	98 % & 100.9%	97.9% & 100.4%	98.6% &101%
Dissolution (till 12 hrs) [Boswellia serrata & Ginger]	-	82.32% & 98.98%	83.56% & 98.41%	84.65% & 99.12%
Lag time (hours)	-	4	4	4

Table 25. Two month stability data at 40±2°C and 75±5% RH

Tests	Specification	Initial	1 Month	2 Month
Description	Yellowish brown coloured caplet	Yellowish brown coloured caplet	Yellowish brown coloured caplet	Yellowish brown coloured caplet
Weight (mg)	825±5% mg	825-827	827-828	827-828
Thickness (mm)	-	6	6	6
Hardness (kg/cm^2)	-	5	5	6
Assay (%) [Boswellia serrata & Ginger]	-	99 % & 98.45%	98.1% & 100.9%	99.5% &101%
Dissolution (till 12 hrs) [Boswellia serrata & Ginger]	-	81.21% & 97.8%	82.56% & 97.21%	81.65% & 97.12%
Lag time (hours)		4	4	4

There is no significant change in the dissolution profile, appearance and weight of tablet. The colour of the tablet gets darker over time. The long term data for any attribute did not show any significant change over time, hence the formulation will remain within the acceptance criteria during the proposed shelf life.

There is no significant change in the dissolution profile, appearance and weight of tablet. The colour of the tablet gets darker over time. The accelerated data for any attribute did not show any significant change over time, hence the formulation will remain within the acceptance criteria during the proposed shelf life.

CONCLUSION:

The formulation of chronotherapeutic release tablets for rheumatoid arthritis was formulated to reduce the side effects of the local NSAID's and to provide better targeted drug delivery at the proper chronobiological period. In-vitro drug release study showed sustained release of formulation for 12 hours. Thus, the use of chronotherapeutic tablets may be considered as a promising, safe and efficacious approach for targeted oral drug delivery of Boswellia serrata and ginger, and thus, providing successful treatment of Rheumatoid Arthritis.

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