Research Article

An In vitro Investigation of Suitability of Press-Coated Tablets with Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) in Outer Shell for Colon Targeting

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ABSTRACT

The aim of present study was to develop a new colon targeting formulation, which can minimize the escape of Mesalazine completely in upper gastro-intestinal tract and ensure availability of maximum amount of drug to achieve the desired site i.e. distal colon. The use of press coated tablets with Hydroxypropylmethylcellulose acetate succinate (HPMCAS) in outer shell was investigated. Two coats (upper and lower) were compressed onto the core tablets of Mesalazine using varying quantities of coating composition i.e. 100mg and 150mg each for lower and upper coat. The Mesalazine tablets coated by compressing 100 mg of HPMCAS each as upper and lower coat did not maintain integrity of the coats and released almost 100% of drug within 3 hrs. The tablets coated by compressing 150 mg of HPMCAS on the core tablets maintained good integrity during the dissolution test and prevented escape of Mesalazine totally in acid stage and buffer sage 1. However, the release of Mesalazine in subsequent buffer stage 2 was also affected. The amount of Mesalazine released from the tablets coated with higher proportion of HPMCAS was compared with marketed tablet (Asacol)*. These release indicating the usefulness of press coated tablets.

Keywords: compression coating, Mesalazine, ulcerative colitis. HPMCAS, granulation.

INTRODUCTION

Colonic drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases of colon such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis (UC) but also for its potential for the delivery of proteins and therapeutic peptides like insulin[1]. Inflammatory Bowel Diseases (IBD) includes two conditions Ulcerative colitis and Crohn's disease. Ulcerative colitis (UC) is a condition that affects a part of large intestine–the rectum and the colon[2]. The affected part becomes inflamed and develops ulcers, causing symptoms that include bloody diarrhoea, abdominal pain and fever. Mesalazine is considered to be the "Gold standard" drug for treatment of ulcerative colitis and it is available as delayed released tablets, controlled released capsules, enteric coated tablets for oral use and rectal suppositories, enema suspension for rectal use[3].

In present study, press coated tablets were prepared using Hydroxypropylmethylcellulose acetate succinate (HPMCAS) as a basic enteric material in the outer shell, and their functions were examined by in vitro dissolution test. In addition the comparative study done with release of marketed tablet (Asacol)* The release profile were found to be improve the acid resistance and time released function of press coated tablet using HPMCAS[4].

MATERIAL AND METHODS

Mesalazine was obtained from Sarex Overseas, Mumbai, India, HPMCAS, povidone (PVP-K30) and microcrystalline cellulose from Signet chemical corporation, Mumbai for free of cost. Talc and Magnesium stearate were procured from Emcure House M.I.D.C. Pune. All the other chemicals and reagents used were of analytical grade. The commercially available Mesalazine product, Asacol was procured from A. Birla hospital (Pune).

Formulation of compression coated tablets of Mesalazine

The formulation was developed in two stages. Initially the core tablets (weight 300mg) of Mesalazine were prepared using following formula. (Table 1) Subsequently two coatings were compressed onto these cores (upper layer and lower layer) using S.S. punches (diameter 13 mm flat surface) on rotary tablet press. The compression force was maintained

in such a way that the hardness of resulting core tablets ranged between 2-3 Kg / m2[5].

Preparation of core tablets of Mesalazine

The physical mixtures of polymers and excipients were prepared by blending the accurately weighed quantities of each of them with Mesalazine in geometric proportions in glass mortar for 15 minutes.

Ethnolic solution of PVP K-30 (3% w/v) was used as binder which was added gradually to powder blends with trituration until a coherent moist mass was formed. This mass was passed through screen (22#) to get moderately coarse granules.

The wet granules were dried at 50˚C.for 1 hour. The dried granules were again passed through screen (44#) to obtain fine granules. The resulting granules were lubricated with magnesium stearate. (Table 1)

For the preparation of Core tablets (300 mg), tableting was performed under compression force of 1030kg/cm^2 and punch speed of 10 mm/min, with a multi station rotary punch tablet compression machine. A flat faced punch 8 mm in diameter was used[6].

Table 1: Formulae for Mesalazine core tablets

Formulation code	Tablet excipients (%w/w)			
	Povidone (PVP K-30)	Ac-Di-Sol	Magnesium stearate	Talc
C1	3	0	1	12.67
C2	3	1	1	11.67
C3	3	2	1	10.67
C4	3	3	1	9.67
Total weight of core tablet= 300mg				

The drug contents were maintained at 250 mg for all the formulations

Evaluation of core tablets

The core tablets were evaluated for various tablet characterization viz;

Tests for physical evaluation Tests for performance evaluation

- Appearance & dimensions
  1. Test for % drug content
- Weight variation
  2. In-vitro drug release
- Hardness
- Friability

Test for physical evaluation of core tablets were carried out by the procedure described in standard text book Liberman, 200[7].

***In vitro* release of Mesalazine from core tablets**

The test was conducted using three tablets of each type of formulation using USP (23) dissolution apparatus (Apparatus I)[8]. The test was performed using 900 ml of phosphate buffer (pH 7.2). Aliquots were withdrawn at time intervals of 5 minutes carefully over a period of 60 minutes. Every time the equal volume of fresh dissolution medium, (maintained at same temperature) was added to the bulk to maintain sink conditions. Samples were filtered through whatman filter paper (No. 41) and their absorbances were recorded at λmax 303.5nm[9].

Coating of core tablets using different polymer compositions

The coating formulae were prepared using HPMCAS (HF) in different proportions (Table.2)

Table 2: Composition of compression coated tablets

Code for coated Tablets	Coating layer composition
CHA1	100 mg each layer
CHA2	150 mg each layer

Compression of coats on core tablets of Mesalazine

Two coats (upper and lower) were compressed onto the core tablets of Mesalazine using varying quantities of coating composition i.e. 100mg each for lower and upper coat; 150mg each for lower and upper coat.

Evaluation of coated tablets of Mesalazine

The coated tablets were evaluated for the various physical and performance

characteristics similar to the core tablets of Mesalazine.

- ***In vitro* release of Mesalazine from press coated tablets**

The test was conducted using three tablets of each type of formulation using USP (23) dissolution apparatus (Apparatus I)[8].

Table 3: The experimental conditions used for *in vitro* release of Mesalazine from press coated tablets

Phases	Type and volume of dissolution medium	Speed of rotation (rpm)	Duration (min)	λ max used for recording absorbance	Volume withdrawn &frequency of withdrawn of aliquots
Phase I Acid stage	0.1N HCl 500ml pH- 3	100 rpm	120	303.0	10ml at intervals of 30min
Phase II Buffer stage-1	phosphate buffer 900ml pH- 6	100 rpm	60	330.0	10ml at intervals of 30min
Phase III Buffer stage-2	phosphate buffer 900ml pH-7.2	50 rpm	90	331.0	10ml at intervals of 30min

Procedure

The tablets of each type of formulations were kept in baskets which were placed successively in above mentioned dissolution media. The dissolution apparatus was run maintaining above stated test conditions. (Table 3)

- In the phase I, the test was performed using 0.1N HCL.10 ml aliquots were withdrawn at time intervals of 30 minutes carefully over a period of 120 minutes. Every time the equal volume of fresh dissolution medium, (maintained at same temperature) was added to the bulk to maintain sink conditions. Samples were filtered through Whatman filter paper (No. 41) and their absorbances were recorded at λmax 303.5nm.
- In the phase II i.e. buffer stage-1, 900 ml of phosphate buffer (pH 6) was transferred into each of the dissolution vessels. Apparatus was run maintaining test conditions as mentioned for buffer stage-1. Aliquots (10ml) were removed after 30 minutes carefully over a period of 60 minutes and were filtered and absorbances were recorded at λ max 330.0nm. Equal volume of phosphate buffer (pH 6) was added into the vessels after each withdrawal.
- In the phase III i.e. buffer stage-2, 900 ml of phosphate buffer (pH 7.2) was transferred into each of the dissolution vessels. Apparatus was run again maintaining test conditions as mentioned for buffer stage 2. Aliquots (10 ml) were withdrawn at time intervals of 30 minute carefully over a period of 90 minutes. Every time the equal volume of fresh dissolution medium, (maintained at same temperature) was added to the bulk. These samples were filtered through Whatman filter paper (No. 41) and their absorbances were recorded at λ max 331.0 nm.

RESULT AND DISCUSSION

Characterization of lubricated granules of Mesalazine used for core tablets

The values for loose bulk density, tapped bulk density, compressibility index and angle of repose of granules of Mesalazine prepared with PVP K-30 as binder for core tablets indicated good flow properties. (Table 4).

Table 4: Flow properties of granules of Mesalazine

Code	LBD (g/ml)	TBD(g/ml)	Carr's C.I. (%)	Angle of repose(Ø)
C1	0.22±0.04	0.26±0.03	15.38±0.42	24.22
C2	0.24±0.05	0.29±0.01	17.24±0.56	24.32
C3	0.24±0.03	0.28±0.05	14.28±0.54	24.69
C4	0.21±0.02	0.25±0.02	16.00±0.40	25.40

All values are expressed as mean± SD, n=3

Values of loose bulk density and tapped bulk density for Mesalazine granules ranged between 0.21±0.02- 0.24±0.05 and 0.25±0.02- 0.29±0.01 g/ml. Similarly values of Carr's index ranged between 15.38±0.42- 16.00±0.40. Angle of repose values ranged between 24.22-25.40 suggesting good flow properties of granules.

Table 5: Characterization of core tablets of Mesalazine

code	Avg. weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)
C1	299±1.56	8.09	3.12	2.0	0.83	99.42±0.123
C2	300±0.85	7.96	3.10	2.0	0.88	99.45±0.066
C3	297±1.92	7.90	3.13	2.5	0.76	98.35±0.107
C4	300±2.25	8.02	3.10	3.0	0.74	98.26±0.126

The core tablets possessed acceptable values for tablet characteristics.

- **Effect of varying concentrations of superdisintegrant on *in vitro* release of Mesalazine from core tablets**

In vitro dissolution data of Mesalazine from the control tablets i.e tablets prepared without addition of superdisintegrant indicated complete release of the drug within 65 minutes in the buffer stage 2 while the core tablets containing increasing concentrations of superdisintegrant released the contents in shorter span of time period. Thus, the tablets containing highest % (3%w/w of tablet weight) amounts of Ac-di-Sol released Mesalazine within 40 minutes in the buffer stage 2 (Table 6; Fig 1).

Table 6: Dissolution data Mesalazine from the core tablets

Time (min)	Cumulative (Avg.) % drug release from core tablets.			
	C1	C2	C3	C4
0	0	0	0	0
5	16.83±0.98	15.358±1.36	28.52 ±1.06	32.55±1.77
10	21.21±1.23	24.74±1.46	45.27 ±1.53	55.09±0.89
15	24.16±1.52	21.40±1.82	58.67 ±2.25	75.16±2.13
20	29.99±1.36	37.46±2.01	70.70 ±1.51	83.43±0.79
25	34.56±1.63	47.66±2.75	79.64 ±1.90	87.86±1.18
30	43.08±2.35	58.16±2.17	81.71 ±0.88	92.33±1.57
35	50.65±3.01	66.65±1.35	89.44 ±1.46	95.42±1.11
40	56.28±1.42	74.53±1.21	93.717±1.99	98.54±2.20
45	63.54±1.49	82.89±1.02	99.63 ±2.38	--
50	71.81±2.31	90.03±0.99	--	--
55	80.21±3.08	98.34±1.46	--	--
60	91.51±1.35		--	--
65	98.56±2.11	--	--	--

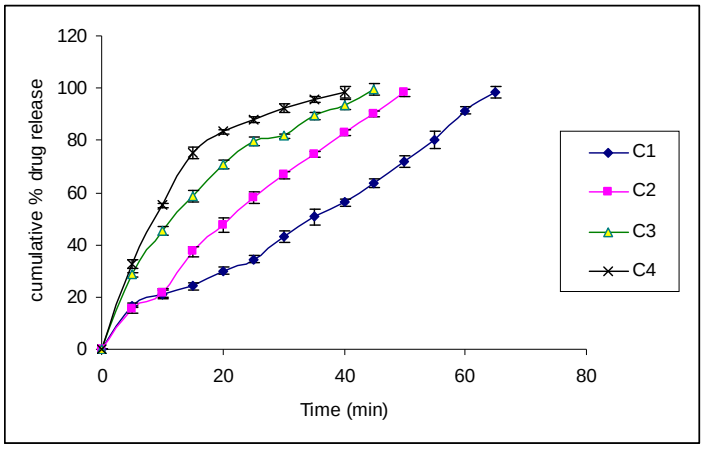

Fig. 1: *in vitro* release of Mesalazine from core tablets

Characterization of compositions used for coating of the core tablets of Mesalazine

Values of loose bulk density and tapped bulk density for HPMCAS used for coating the core tablets were greater than those required for good flowability. Similar observations was made for the angle of repose of the blends prepared using HPMCAS. (Table 7).

Table 7: Tablet characteristics of coated tablets of Mesalazine with varying amounts of coating formulae

code	Avg. weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)
CHA1	499±1.56	12.67	3.37	8.0	0.52
CHA2	600±0.85	12.73	3.64	8.0	0.58

Characterization of coated tablets of Mesalazine

- The pharmacopoeial specifications for deviation in weight from average weight for tablets weighing more than 250 mg are ±5%. The percentage deviation in the weight of prepared tablets (weighing 600 mg except CHA1 weighing 500 mg) was within the specified limits for all the formulations and hence they complied with the test for weight variation
- There was obvious increase in diameter, thickness and hardness of the coated tablets as compared with core tablets.
- The friability of all the coated formulations was lower than the core tablets and complied with the specified limits.

***In vitro* release of Mesalazine from prepared compression coated tablets**

- The Mesalazine tablets coated by compressing 100 mg of HPMCAS each as upper and lower coat did not maintain integrity of the coats and released almost 100% of drug within 3 hrs. This performance is not useful to qualify these tablets as colon targeted formulations (Table 8).
- The tablets coated by compressing 150 mg of HPMCAS on the core tablets maintained good integrity during the dissolution test and prevented escape of Mesalazine totally in acid stage and buffer sage 1. However, the release of Mesalazine in subsequent buffer stage 2 was also affected (Table 8; Fig 2).

Table 8: *In vitro* release data of Mesalazine from experimental coated tablets with HPMCAS

Time (min)	C4 (core tablet)	Dissolution phase	Cumulative % drug release		
			Time (min)	CHA1	CHA2
0	0	Acid stage pH 3	0	0	0
5	32.55±1.77		30	2.501±.0.38	0.025±0.21
10	55.09±0.89		60	47.88±.0.86	0.034±0.58
15	75.16±2.13		90	61.34±.0.98	0.45±.094
20	83.43±0.79		120	79.27±1.28	**0.98±1.28**
25	87.86±1.18	Buffer stage 1 pH 6.0	150	90.61±2.54	2.198±1.11
30	92.33±1.57		180	98.87±2.14	**6.451±2.14**
35	95.42±1.11	Buffer stage 2 pH 7.2	210	-	19.73±2.84
40	98.54±2.20		240	-	37.21±3.10
--	--		270	-	76.37±2.14
--	--		300	-	**88.12±1.47**
--	--		330	-	98.47±1.34

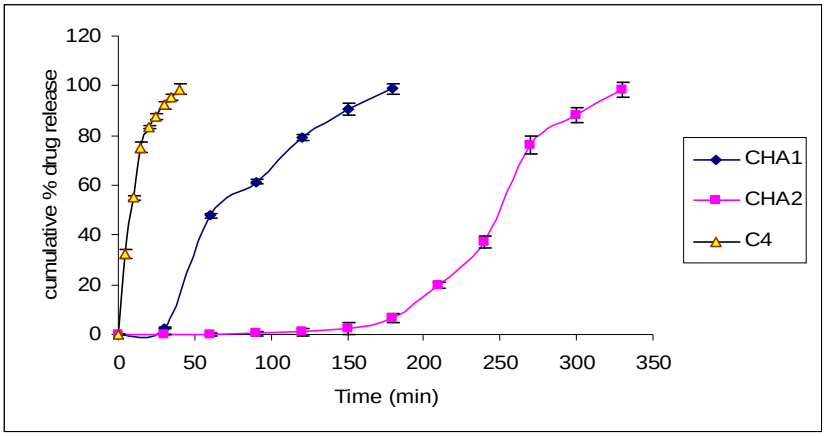

Fig. 2: *In vitro* dissolution profiles of Mesalazine from experimental coated tablets

Comparative evaluation of HPMCAS press coated tablets with marketed product Asacol*

The comparison of in vitro release profile of the formulation with those of the commercial product Asacol showed that the press coated tablets released 0.98% of drug during the first two hours, in acidic phase and 6.451% in buffer stage 1 at pH-6. No mesalazine release was found from Asacol* (Table 9; Fig 3). The increasing amount of HPMCAS in outer press coat results in the prevent the release of drug effectively in buffer stage II at pH 7.2 compared with marketed product Asacol*.

Table 9: Comparative evaluation of HPMCAS press coated tablets with markated product Asacol*

Dissolution phase		Cumulative % drug release		
	Time (min)	Asacol*	CHA1	CHA2
Acid stage pH 3	0	0	0	0
	30	0	2.501±.0.38	**0.025±0.21**
	60	0	47.88±.0.86	**0.034±0.58**
	90	0	61.34±.0.98	**0.45±.094**
	120	0	79.27±1.28	**0.98±1.28**
Buffer stage 1 pH 6.0	150	0	90.61±2.54	**2.198±1.11**
	180	0	98.87±2.14	**6.451±2.14**
Buffer stage 2 pH 7.2	210	0.73	-	**19.73±2.84**
	240	1.147	-	**37.21±3.10**
	270	42.18	-	**76.37±2.14**
	300	79.82	-	**88.12±1.47**
	330	--	-	**98.47±1.34**

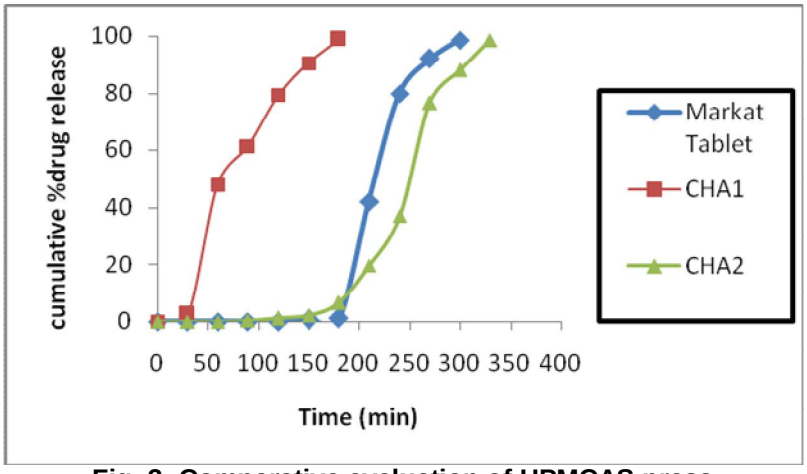

Fig. 3: Comparative evaluation of HPMCAS press coated tablets with marketed product Asacol*

CONCLUSION

The applicability of press-coated tablets for colon targeting delivery systems, which suppress drug release totally in acid stage and buffer sage 1, was studied using hydroxypropylmethylcellulose acetate succinate (HPMCAS) an enteric polymer in two proportions in outer shell. The Mesalazine tablets coated by compressing 100 mg of HPMCAS each as upper and lower coat did not maintain integrity of the coats and released almost 100% of drug within 3 hrs. This performance is not useful for qualifying colon targeting drug delivery. The tablets coated by compressing 150 mg of HPMCAS on the core tablets maintained good integrity during the dissolution test and prevented escape of Mesalazine totally in acid stage and buffer sage 1. Comparative study of press coated tablets with marketed formulation (Asacol) indicated the usefulness of it for colon targeted delivery.

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