Original Research Article

Development and evaluation of 6-mercaptopurine and metoclopramide polypill formulation for oral administration: *In-vitro* and *ex vivo* studies

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Abstract

Introduction: The present investigation was to develop a polypill of 6-mercaptopurine and metoclopramide. A polypill with delayed release granules of an anticancer and immediate release mucoadhesive tablet of antiemetic may result in the reduction of emesis caused by oral chemotherapy. **Materials and Methods:** 6-Mercaptopurine granules were prepared by wet granulation process. Chitosan, hydroxypropyl methylcellulose, and ethylcellulose were used as individually as delayed release polymers. Seven granule formulations (F1-F7) were prepared and evaluated for flow properties and drug content. Immediate release mucoadhesive tablets of metoclopramide were prepared by direct compression technique using pectin and PVPK-40 as mucoadhesive polymers. Three formulations of pectin (L1-L3) and three formulations of PVPK40 (M1-M3) were prepared using lactose, magnesium stearate, and mannitol and talc as diluent and glidant, respectively. Tablets were evaluated for weight variation, hardness, friability, drug content, *ex vivo* mucoadhesion time, and *in vitro* dissolution studies. **Results:** Formulation F2, F4, F5, and F7 showed maximum drug content. Formulation F7 exhibited the drug release up to 2 h and was selected as the best delayed release formulation. All formulations of metoclopramide showed good drug content ranging from 97.6 % to 100.6%. Formulation M2 among tablets prepared with PVP exhibited desired mucoadhesion time of 15.33 min which prolongs the duration of drug release in gastric pouch of the male Wistar rats. Both the selected formulations F7 and M2 were filled into body of capsule size 0 and capsule was evaluated for technological properties. **Conclusion:** It may be concluded that polypill released the metoclopramide immediately prior to 6-mercaptopurine.

Key words: 6-mercaptopurine, delayed release, immediate release, metoclopramide, polypill

INTRODUCTION

Cancer is a disease that begins in the cells of the body. In usual situations, the cells grow and segregate as the body needs them. This orderly course of action is disturbed when new cells form which the body does not need and old cells do not die when they should. These extra cells lump jointly to form a growth or tumor.[1] There are two common approaches used to treat almost all types of cancer are chemotherapy and radiotherapy. Chemotherapy is one of the most commonly used methods to treat cancer patients. Chemotherapy can be used to reduce the symptoms and pain associated with cancer as well as to slow the growth of cancerous tumours.

In addition to cancerous cells, chemotherapy drugs also kill some regular healthy cells, causing side effects such as the fatigue, nausea, and vomiting and hair loss.[2]

6-mercaptopurine is an anticancer agent with an elimination half-life of 1.5 h, which may result in decreasing of the therapeutic potential and presenting such side effects as severe bone marrow depression and gastrointestinal damage. One of the possible approaches for overcoming these disadvantages and improving the chemotherapeutic activity is the sustained release dosage form.[3]

Chemotherapy-induced nausea and vomiting (CINV) are two greatest fears of patients with cancer. Inadequately controlled CINV can precipitate a number of medical complications that may prove life-threatening, as well as dehydration and electrolyte imbalance, or cause physical damage.[4,5]

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Access this article online

Quick Response Code:

Website: www.jpionline.org

DOI: 10.4103/2230-973X.121306

Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane. Mucoadhesive polymers facilitate the mucoadhesion by their specific properties.[6]

Metoclopramide hydrochloride is a potent antiemetic effective in the treatment of nausea and vomiting associated with cancer therapy, pregnancy, migraine, and so on.[7]

A polypill is a medication which contains a combination of active ingredients as separate dosage form in a single unit with the intention of reducing the number of tablets or capsules that need to be taken.[8]

In this research work, a polypill consisting of immediate release mucoadhesive tablet of antiemetic, metoclopramide, and delayed release granules of anticancer drug, 6-mercaptopurine was formulated. The mucoadhesive tablets of metoclopramide adhere to the gastrointestinal mucosa and then release the drug. Thus, initiating the antiemetic action prior to the release of 6-mercaptopurine. The delayed release granules of 6-mercaptopurine releases the drug after a time gap and an attempt was made in this polypill, to reduce the CINV by orally administered 6-mercaptopurine.

MATERIALS AND METHODS

6-mercaptopurine was received as gift sample from M/S Aldrich, Bangalore, India. Metoclopramide was provided ex-gratis by M/S Gilman Laboratories. Chitosan and hydroxypropyl methylcellulose (HPMC) were gifted by Loba Chemi, Mumbai, Maharashtra, India. Ethyl cellulose and pectin were obtained by Titan Biotech, Bhiwadi (Karnataka, India) and lactose was obtained by M/S Thomas Baker, Mumbai, Maharashtra, India. All other chemicals and reagents were of analytical grade.

Preparation of delayed release granules of 6-mercaptopurine

6-mercaptopurine granules were prepared by wet granulation process. Chitosan, HPMC, and ethylcellulose were used individually for delayed release. Lactose was used as diluent is given in Table 1. A total of 50% alcohol was used as granulating agent. All the powders were dry sieved using sieve No. 16. Required quantities of drug and polymer ware taken in a mortar and mixed. Then the powdered mass was wetted with 50% alcohol. Further, the obtained cohesive mass was passed through sieve no 16. The granules were air dried (25 ± 3°C). The dried granules were regranulated using sieve # 16/22.

Table 1: Formulation of 6-mercapotpurine delayed release granules

S. No	Ingredients*(mg)	F1	F2	F3	F4	F5	F6	F7
1	Mercaptopurine	50	50	50	50	50	50	50
2	Chitosan	75	175	-	-	-	-	-
3	HPMC	-	-	50	150	-	-	150
4	Ethylcellulose	-	-	-	-	50	125	50
5	Lactose	125	25	150	50	150	75	-

*Per 250 mg of granules. HPMC=hydroxypropyl methylcellulose

Evaluation of delayed release granules

Angle of repose

The angle of repose was determined according to the fixed funnel method. Angle of repose (θ°) was calculated from the standard trigonometric relationship.[9]

Bulk density

Both loose bulk density and tapped bulk density were determined. A quantity of 2 g of granules from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 s interval. The tapping was continued until no further change in volume was noted.

Drug content of 6-mercaptopurine

Granules equivalent to 50 mg of drug were taken and dissolved in 0.1 N NaOH in 100 mL volumetric flask. Drug concentration in the sample was measured with ultraviolet (UV) spectrophotometer at 310 nm following appropriate dilutions. All the granule formulations F1-F7 were evaluated for the above three parameters.

Based on the above evaluation formulations, F4 and F7 were found to be most satisfactory and further evaluated for dissolution studies, Fourier transform infrared (FTIR) studies and differential scanning calorimetric (DSC) studies.

Dissolution studies

In vitro dissolution studies were performed for formulations F4 and F7 using Electrolab TDT-06PL Dissolution tester USP apparatus type II (paddle type), at a speed of 75 rpm, in 900 mL of dissolution medium of simulated gastric fluid pH 1.2. The temperature was maintained at 37.0 ± 0.5°C. A total of 5 mL of samples were withdrawn at 5, 10, 25, 30, 45, 60, 90, 120 min and was replaced with 5 mL of pH 1.2 buffer after each withdrawal and were analyzed by UV spectrophotometer at 310 nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan). On the basis of the drug release pattern formulation F7 was carried for further evaluation.

FTIR spectroscopy

Infrared (IR) spectra of 6-mercaptopurine, physical mixture, and the F7 formulation were obtained with Shimadzu FTIR-8700 spectrophotometer, using the potassium bromide (KBr) pellet disk technique (about 10 mg of sample for 100 mg of dry KBr) in order to conclude the drug excipient interaction. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded from 4000 to 500 cm^{-1}.

DSC analysis

Differential scanning calorimetry was carried out using DSC Q2000. Samples were weighed (8.00-10.00 ± 0.5 mg) and placed in sealed aluminium pans. The coolant was liquid nitrogen. The

samples were scanned at 100°C/ min from 200°C to 250°C. DSC thermo grams of 6-mercaptopurine, physical mixture, and F7 formulation were taken.

Comparison of in vitro release studies of formulation F7 with marketed formulation

In vitro dissolution studies were performed for marketed conventional tablet formulation of 6-mercaptopurine using Electrolab TDT-06PL Dissolution tester USP apparatus type II (paddle type), at a speed of 75 rpm, in 900 mL of dissolution medium in pH 1.2. The temperature was maintained at 37.0 ± 0.5°C. A total of 5 mL of samples were withdrawn at 5, 10 min and was replaced with 5 mL of pH 1.2 buffer after each withdrawal and were analyzed by UV spectrophotometer at 310 nm (Model UV-1700, UV-Visible spectrophotometer, Shimadzu, Kyoto, Japan). The dissolution data of formulation F-7 obtained was compared with the data of marketed formulation.

Preparation of immediate release mucoadhesive tablet of metoclopramide

Metoclopramide tablets were prepared by direct compression technique. Pectin and PVP K40 were used as mucoadhesive polymers. Three formulations (L1-L3) of pectin using lactose as diluent and magnesium stearate as glidant were prepared [Table 2]. Further, three formulations (M1-M3) of PVPK40 using mannitol as diluent and talc as glidant were prepared is shown in Table 2. The drug and excipients were added in geometric progression and blended to obtain uniform mixing. The blended powder was evaluated for flow properties. Then, the powder blend was compressed on CIP tablet machine (CIP Punching Machineries Pvt. Ltd, Mumbai, Maharashtra, India) using 6 mm punch with 10 punch station).

Evaluation of powder blend

Angle of repose, bulk density

The powders were evaluated for their flow properties as described in previous section.

Evaluation of tablets

The directly compressed tablets were evaluated for weight variation test, hardness, friability, disintegration test, drug content, DSC studies, *in vitro* mucoadhesion time, and *in vitro* dissolution studies.

Table 2: Formulation design of metoclopramide tablets with pectin and PVP K40

Ingredients (per tablet in percentage)	L1	L2	L3	M1	M2	M3
Metoclopramide*	10	10	10	10	10	10
Pectin	40	50	60	-	-	-
PVP K40	-	-	-	30	40	50
Lactose	45.5	35.5	25.5	-	-	-
Mannitol	-	-	-	57	47	37
Magnesium stearate	2	2	2	-	-	-
Talc	-	-	-	3	3	3
Total weight (mg)	80	80	80	80	80	80

Metoclopramide* mg/tablet

Weight variation test

A total of 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method I.P.

Hardness and friability

For each formulation, the hardness and friability of six tablets were determined using the Monsanto hardness tester and the Roche friabilator, respectively.

Disintegration test

Disintegration time of the different formulations was determined using Electrolab disintegration test apparatus. Apparatus was operated using pH 1.2 buffer as medium, maintained at 37 ± 2°C.

Drug content of metoclopramide

A total of 20 tablets were prepared and sample equivalent to 10 mg of the drug was dissolved in methanol. The samples were analyzed by UV following procedure described above. Absorbance was measured at 275.6 nm using UV spectrophotometer. The experiment was carried out in triplicate.

Ex vivo mucoadhesion test

The gastric pouch of the male Wistar rats of 3 months old was used. The experimental protocol was approved by the institutional animal ethical committee. The animal was sacrificed by cervical dislocation. The abdominal portion of the animal was dissected and the gastric pouch was collected and kept in physiological salt solution. It was further used for *ex vivo* mucoadhesion test. The mucoadhesive performance of the tablets was evaluated by assessing the time for the tablets to detach from the gastric pouch membrane in a well-stirred beaker. The gastric pouch membrane was fixed on the side of the beaker with cyanoacrylate glue. The tablets were attached to the membrane by applying light force with fingertip for 30 s. The beaker was then filled with 500 mL gastric buffer pH 1.2 maintained 37°C. A stirring rate of approximately 75 rpm was used to stimulate gastric movement.[10]

On the basis of above evaluation, formulation L1 and M2 were found to be most satisfactory and hence were subjected for further evaluation.

In vitro release studies for metoclopramide mucoadhesion tablets

In vitro dissolution studies were performed for L1 and M2 using Electro lab-USP Dissolution test apparatus of paddle type at a speed of 75 rpm. Temperature of 37 ± 0.1°C was maintained in 900 mL of pH 1.2 buffer medium only.[11,12] A total of 5 mL sample was withdrawn every 5, 10, 15, and 20 min and was replaced with 5 mL buffer, after each withdrawal. A total of 5 mL of withdrawn sample was filtered. A total of 1 mL of filtrate was diluted to 10 mL using methanol. Absorbance was measured at 275.6 nm using UV spectrophotometer.

DSC analysis

The experimental method described under section was used for L1 and M2.

Comparison of *in vitro* release studies of formulations L1 and M2 with marketed formulation

In vitro dissolution studies were performed for marketed conventional tablet using Electrolab-USP Dissolution test apparatus of paddle type with RPM of 75. Temperature of 37 ± 0.1°C was maintained in 900 mL of pH 1.2 buffer medium only. A total of 5 mL sample was withdrawn at 5 and 10 min and was replaced with 5 mL buffer, after each withdrawal. A total of 5 mL of withdrawn sample was filtered. A total of 1 mL of filtrate was diluted to 10 mL using methanol. Absorbance was measured at 275.6 nm using UV spectrophotometer. The dissolution data's of formulations L5 and M2 obtained were compared with the data of marketed formulation.

Preparation of drug-loaded polypill

On the basis of bulk density, compressibility index, angle of repose, drug content, and dissolution profile formulation F7 was selected as the best delayed release formulation of 6-mercaptopurine. Formulation M2 was selected as the best formulation of metoclopramide based on friability, hardness, disintegration time, drug content, and mucoadhesion. Both the selected formulations F7 and M2 were filled into body of capsule size 0 and cap was slipped back into the body and both were sealed. In addition, it imparts gloss to the capsules. The capsules were further evaluated for various parameters.

Evaluation of capsules

- Average Weight of Filled Capsule
  20 capsules were weighed; average weight was calculated using the following formula:
  Average weight in g = weight of 20 capsules in g/20.
- Uniformity of Dosage Units (By Weight Variation)
  The uniformity of dosage units can be demonstrated by either of two methods, content uniformity or weight variation.

Procedure

Accurately 20 capsules were weighed individually, taking care of the identity of each capsule. Contents of each capsule were removed by suitable means. Emptied shells were accurately weighed individually. Net weight for each capsule of its contents was calculated by subtracting the weight of the shell from the respective gross weight. Drug content expressed as % of the label claim, for each capsule was calculated from the net weight of individual capsule content and the result of assay.

Uniformity of filled capsule weight

Intact capsule taken for average weight determination was weighed individually and weight recorded in "g." Uniformity of the filled capsule weight was calculated by the formula:

$$\frac{\text{Lowest weight of the filled capsule in g-Average weight}}{\text{Average weight of filled capsule in g}} * 100$$

$$\frac{\text{Highest weight of the filled capsule in g-Average weight}}{\text{Average weight of filled capsule in g}} * 100$$

Disintegration test

Disintegration test apparatus was used to perform the test. One capsule each was placed in each of six tubes of the basket-rack assembly of disintegration test apparatus and discs to each tube. Apparatus was operated using pH 1.2 buffer as medium, maintained at 37 ± 2°C. Assembly was removed from water and time in minutes at which the last capsule disintegrated completely except fragments from the capsule shell was recorded.

Invitro release studies for polypill

In vitro dissolution studies were performed for prepared polypill Capsule Electro lab-USP Dissolution test apparatus of basket type with RPM of 75. Temperature of 37 ± 0.1°C was maintained in 900 mL of pH 1.2 buffer medium. A total of 5 mL sample was withdrawn at 5, 10, 25, 30, 45, 60, 90, and 120 min and was replaced with 5 mL of pH 1.2 buffer after each withdrawal. A total of 5 mL of withdrawn samples were filtered. A total of 2 mL each from the filtrate was analyzed for 6-mercaptopurine and metoclopramide respectively by the methods reported earlier.

Stability studies

Prepared formulation of polypill (capsule) was transferred to amber colored screw capped bottle. It was then placed in humidity control chamber and an accelerated stability condition of 40 ± 2°C/75% RH was maintained. Testing was carried out at 0, 1, 2, and 3 months, respectively. Physical appearance, drug content, and dissolution profile were tested.

RESULTS AND DISCUSSION

Delayed release granules of pure 6-mercaptopurine were prepared. Percentage yield and percentage drug content of 6-mercaptopurine granules were in between 79.81% to 87.86% and 94.13% to 97.86% as shown in Table 3. Whereas formulation F4, F5, and F7 gave maximum yield. Formulation F2, F4, F5, and F7 showed maximum drug content. The flow properties like angle of repose were in between 21.03 and 33.68 and Hausner's ratio was in between 1.025 and 1.063. The flow properties of granules were found to be satisfactory for all formulations except for F1 and F2 shown in Table 4. Formulations F1, F2, and F3 granules were found to be in the powder form which was prepared using chitosan only in low and high percentage and only HPMC in low percentage, whereas F6 granules were hard which were prepared using only ethylcellulose in maximum percentage.

Table 3: Percentage yield and percentage drug content of 6-mercapotpurine granules

Formulation code	% *Yield±SD	% *Drug content±SD
F2	81.48±0.0051	97.68±0.1417
F3	82.28±0.0002	95.83±0.2401
F4	85.68±0.0045	97.62±0.2018
F5	85.35±0.0056	96.68±0.2217
F6	79.85±0.0005	91.86±0.1152
F7	87.86±0.0012	97.86±0.1823

*Average of three determinations. SD=standard deviation

Table 4: Evaluation properties of granules

Formulations	Angle of repose	Loose bulk density	Tapped bulk density	Hausner's ratio
F1	33.68±0.458	0.251±0.007	0.266±0.005	1.063±0.005
F2	32.47±0.532	0.236±0.004	0.248±0.007	1.060±0.006
F3	25.74±0.621	0.297±0.001	0.315±0.001	1.048±0.001
F4	21.03±0.826	0.343±0.005	0.358±0.011	1.043±0.007
F5	22.33±0.718	0.313±0.005	0.333±0.005	1.063±0.005
F6	24.86±0.214	0.424±0.005	0.435±0.006	1.025±0.005
F7	24.37±0.186	0.356±0.004	0.369±0.005	1.036±0.004

*Average of three determinations

Dissolution profiles of the formulation F4 which was prepared using HPMC alone in high percentage exhibited the drug release up to 90 min. The dissolution profile of the formulation F7 which was prepared using HPMC in high percentage in combination with ethylcellulose in low percentage exhibited drug release up to 2 h. Dissolution data of F7 found to be more satisfactory as compared to formulation F4 and marketed formulation as shown in Figure 1.

The IR spectrum of pure 6-mercaptopurine [Figure 2] revealed the presence of a peak at 3433 cm^{-1} due to N-H stretching, while peak at 771 corresponded to -SH bending. Strong absorption peaks observed at 1410 cm^{-1} are assigned to drug cyanide functional group (C = N). The rest of the fingerprint absorption bands appear at 1008.7, 933.48, 867.91, 771.47, 675.04, 646.11, 588.25 cm^{-1}. Physical mixture of the drug, HPMC, and ethylcellulose. Figure 2 showed summation of the spectra of the drug and HPMC and ethylcellulose equivalent to the addition of the spectrum of polymer and drug. This indicates that there was no considerable interaction between simple physical mixture of drug and polymer.

In case of granules of the 6-mercaptopurine with HPMC and ethylcellulose, Figure 2 showed peak at 3320 cm^{-1}, that is, N-H stretching is shifted to lower wave number. At the same time other characteristic peaks of drug such as 718, 1407, 3024 cm^{-1} corresponding to S-H stretching, C = N stretching, C-H-Ar group stretching remain unchanged. This indicated that overall symmetry of the molecule might not be significantly changed.

DSC thermogram of 6-mercaptopurine, Figure 3 showed an endothermic peak at 314°C corresponding to the melting point of 6-mercaptopurine. In case of physical mixture of 6-mercaptopurine and HPMC [Figure 3] systems, it was seen that drug peak intensity was reduced. In case of physical mixture of 6-mercaptopurine, HPMC, and ethylcellulose [Figure 3] it was seen that the shift of endothermic peak of 6-mercaptopurine to slightly higher temperature.

Granules of 6-mercaptopurine [Figure 3] showed that drug peak intensity was reduced further, compared to physical mixture of HPMC and ethylcellulose. This indicated that 6-mercaptopurine crystallinity was reduced and might have got converted into the amorphous form.

The immediate release mucoadhesive tablets of metoclopramide were prepared. The powder blend of metoclopramide with excipients showed angle of repose ranging from 30.22 to 31.46. Whereas Hausner's ratio and Carr's index were in the range. The flow properties of the metoclopramide powder blend were suitable for direct compression of tablets as depicted in Table 5.

All formulations of metoclopramide showed good drug content ranging from 97.6% to 100.6% as shown in Table 6. Formulations L1, L2, and L3 were prepared using pectin in combination with lactose showed more friability and less hardness, less disintegration time compared to formulations prepared using PVP in combination with mannitol. When the percentage of pectin increased in formulations L1, L2, and L3, the properties of the tablets like weight variation, hardness, friability, and disintegration time give satisfactory results and exhibited satisfactory results compared with formulations prepared with constant lactose percentage. L1 showed less friability (0.356%), satisfactory hardness (2.38 kg/cm^2), and disintegration time of 4.5 min. L1 was the best formulation among the tablets prepared using pectin with lactose.

The tablets prepared using PVP with mannitol exhibited desired hardness, friability, and disintegration time. Formulation M2 was found to be the best formulation prepared from PVP in combination with mannitol. M2 exhibited desired hardness (4.13 $kgcm^2$), friability (0.178%), and disintegration time (6.01 min). PVP formulations exhibited good results when compared to pectin formulations.

In vitro mucoadhesion time was more for the metoclopramide formulations prepared with PVP compared with formulations prepared with pectin. L5 among the tablets prepared with pectin exhibited satisfactory mucoadhesion time of 5.20 min. Whereas formulation M2 among tablets prepared with PVP exhibited desired mucoadhesion time of 15.33 min which prolongs the duration of drug release.

Dissolution profile of the formulations L1, M2 and marketed formulation were obtained as shown in Figure 4. When compared to dissolution profile of formulations L1 and M2, L1 exhibited compete release of drug in 10 min, whereas formulation M2 exhibited the complete release of drug in 15 min. Formulation M2 was found to be best formulation as compared to L1. The dissolution profile of M2 further compared with the dissolution profile of marketed tablet. The marketed tablet exhibited the

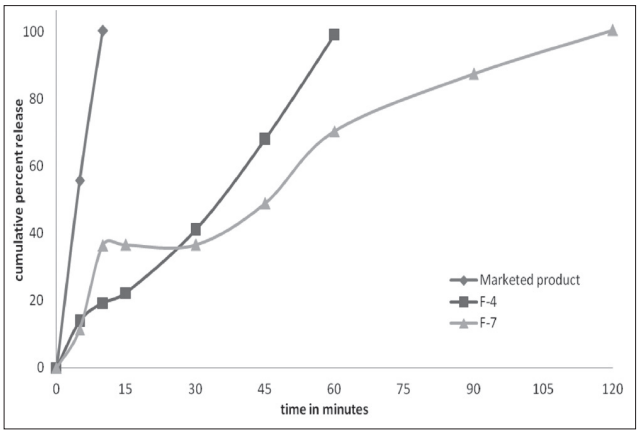

Figure 1: Comparison of dissolution profile of F4, F7 and marketed product

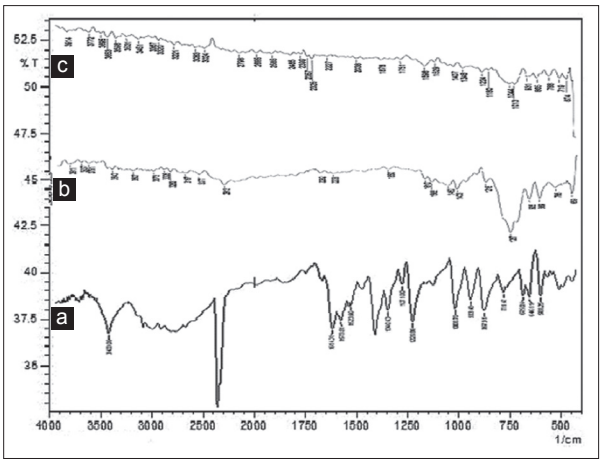

Figure 2: Fourier transform infrared of (a) pure drug, (b) physical mixture, and (c) final formulation F7

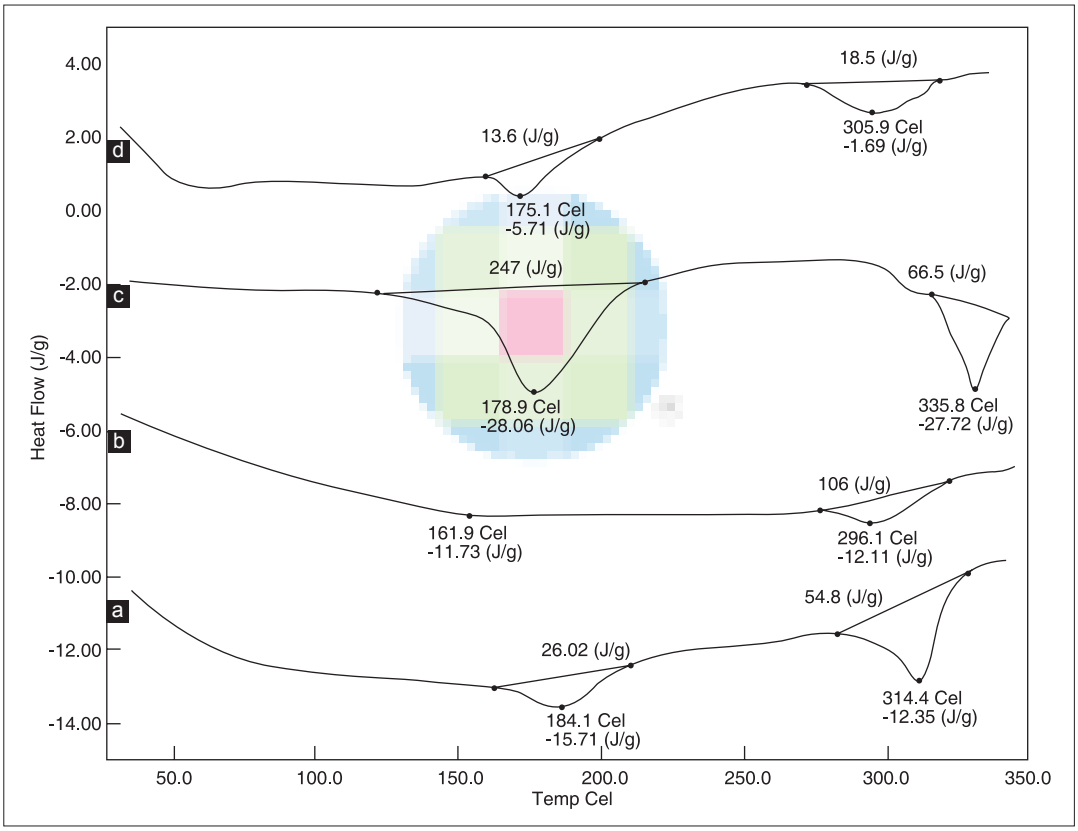

Figure 3: Differential scanning calorimetric of (a) pure drug, (b) physical mixture of pure 6-mercaptopurine and hydroxypropyl methylcellulose (HPMC), (c) Physical mixture of 6-mercaptopurine, HPMC and ethylcellulose, and (d) final formulation F7

Table 5: Evaluation of metoclopramide powder properties

Formulations	*Angle of repose	*Loose bulk density	*Tapped bulk density	Hausner's ratio	*Carr's index (%)
L1	31.60±1.28	0.460±0.022	0.500±0.022	1.087±0.022	7.962±0.351
L2	32.12±1.22	0.476±0.018	0.513±0.015	1.084±0.017	7.534±0.113
L3	32.74±1.18	0.602±0.045	0.645±0.053	1.071±0.048	5.228±0.325
M1	30.48±1.32	0.433±0.009	0.464±0.014	1.071±0.012	6.681±0.175
M2	31.46±0.97	0.443±0.009	0.479±0.017	1.083±0.014	7.515±0.246
M3	30.89±1.56	0.413±0.007	0.452±0.008	1.094±0.075	8.628±0.186

*Average of three determinations

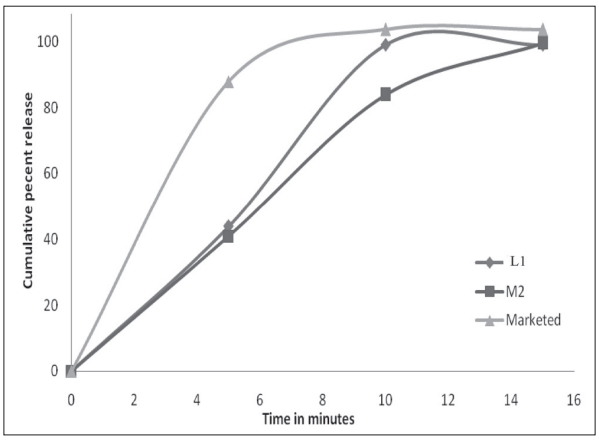

Figure 4: Comparsion of dissolution profile of L1, M2 and marketed formulation

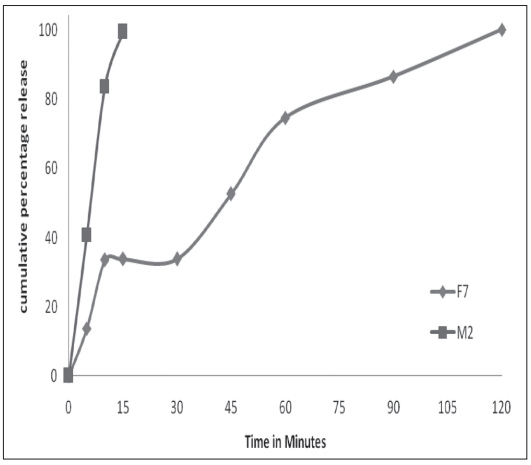

Figure 5: Dissolution profile of polypill formulation

Table 6: Evaluation of metoclopramide tablets

Formulation	*Weight variation (%)	*Hardness (Kg/cm²)	*Friability (%)	*Disintegration time (min)	*Drug content (%)
L1	5.87±0.085	2.38±0.152	0.356±0.0751	4.50±0.570	100.60±0.33
L2	5.21±0.052	2.16±0.152	0.804±0.0744	3.37±0.755	100.03±0.23
L3	6.52±0.045	2.26±0.115	0.792±0.1123	4.00±0.810	99.86±0.15
M1	6.48±0.022	4.26±0.115	0.299±0.0002	5.35±0.395	100.63±1.78
M2	6.52±0.036	4.13±0.115	0.178±0.0003	6.01±0.407	100.12±0.98
M3	6.56±0.56	4.31±0.115	0.096±0.0002	6.49±0.277	99.44±1.19

*Average of three determinations

Table 7: Stability studies of prepared capsule

Sampling interval	% Drug content metoclopramide	% Drug content mercaptopurine	Physical appearance
Initial	100.06	97.86	Characteristic capsule property
1 month	99.54	96.98	No change
2 months	99.26	95.83	No change
3 months	98.21	95.67	No change

complete release of drug in 10 min. M2 was further found to be the best among all formulations.

The disintegration time of polypill was 6.22 min which was most ideal for the proposed formulations. The dissolution profile indicated immediate release of antiemetic metoclopramide within 15 min, whereas the release of anticancer 6-mercaptopurine commenced slowly only after 5 min of time gap as shown in Figure 5. This pattern of release fulfils the immediate release requirement of metoclopramide followed by delayed release of anticancer.

Accelerated stability studies (40 ± 2°C / 75% RH) performed for a period of 3 months and capsules were checked for physical appearance, drug content, and dissolution profile. All the capsules showed no change in physical appearance. There was no noticeable change in drug content and dissolution profile of capsules at the end of 3 months, indicating that the prepared capsules were stable [Table 7].

CONCLUSION

It may be concluded that polypill released the metoclopramide immediately prior to anticancer. Thus, the formulation with immediate release mucoadhesive metoclopramide and delayed release 6-mercaptopurine may be useful as a combination in a polypill. Further, *ex vivo* investigations may prove the possibility of this polypill in reducing orally administered anticancer-induced emesis.

ACKNOWLEDGEMENT

We would like to thank Prof. B. G Shivananda, Principal, Al-Ameen College of Pharmacy and Management Al-Ameen, Bangalore, for their continuous support. We are also grateful to Aldrich and Gilman Laboratories for providing the gift samples of pure drug.

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How to cite this article: Chowdhary R, Pai RS, Singh G. Development and evaluation of 6-mercaptopurine and metoclopramide polypill formulation for oral administration: *In-vitro* and *ex vivo* studies. Int J Pharma Investig 2013;3:217-24.
Source of Support: Nil. **Conflict of Interest:** None declared.