Development of Mucoadhesive Sustained Release Matrix Tablets of Methimazole for oral Delivery

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ABSTRACT

The aim of the present investigation was to develop sustained release matrix tablets containing methimazole. The different batches were manufactured by direct compression method using hydrophilic swellable carbopol and ethocel and eudragit RL100 in combination using Minipress and characterized by FTIR, DSC, *in vitro* mucoadhesion, *in vitro* swelling, erosion and *in vitro* drug release and stability studies. It was found that, the formulation batch MT 6 has a mucoadhesion force about 14.813 ± 0.085 N. It has exhibited the adhesion retention time about 11.16 ± 0.10 h in the entire region of GIT with maximum swelling up to 59.52 ± 4.93 %. It is revealed that drug release by both mechanism diffusion and erosion. Carbopol 934P along with Eudragit RL100 and ethyl cellulose was found to be controlling the release rate of methimazole in matrix tablets for 20 h. It can be concluded that, there is promising potential for this system that can control the release up to 20 h and extend the drug release.

Key words: Carbopol 934P, Eudragit RL100, Ethyl cellulose, Methimazole, Matrix tablet, Percent swelling, Sustain release.

INTRODUCTION

The considerable growth and development in sustained release dosage form (SRDF) can be attributed to several advantages that, these products offer, improved patient compliance, therapeutic efficiency, control of plasma drug levels and less frequent dosing, potential for cost saving and patentability, and opportunity for extending product life-cycle.[1,2] As pharmaceutical research view, numerous types of polymers are currently employed to control the drug release from the pharmaceutical dosage form. Oral sustained release systems are mainly grouped into three types, (e.g.) reservoir, monolithic and matrix types.[3-5]

Carbomers are synthetic, high molecular weight cross linked polymer of acrylic acid. The hydrophilic nature and highly cross linked structure render them more suitable potential candidate for use in controlled drug delivery. The hydrophilic polymer carbopol 934 has a good gel-forming ability and mucoadhesive property that can be used for formulating the SRDF.[6-8] However, the use of hydrophilic polymer alone for controlling the drug release of highly water-soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer and use of the hydrophobic polymers could retard the drug release.[9]

Eudragit RS and RL are biocompatible copolymers synthesized from acrylic and methacrylic acid esters, their permeability to water is unaffected by pH. The acrylate and methacrylate polymer have been used in the preparation of matrix tablets for oral sustained release, tablet coating and microencapsulation of drugs.[10-13]

Ethyl cellulose is a water-insoluble and pH-independent polymer and has been widely used in the prepared SRDFs of a water-soluble material. It used extensively as a coating material, as a tablet binder, in microcapsules (microspheres) and in the preparation of matrix-type controlled release tablets.[14-16]

Methimazole the drug with short half-life of 4-6 hours has used due to well tolerated by

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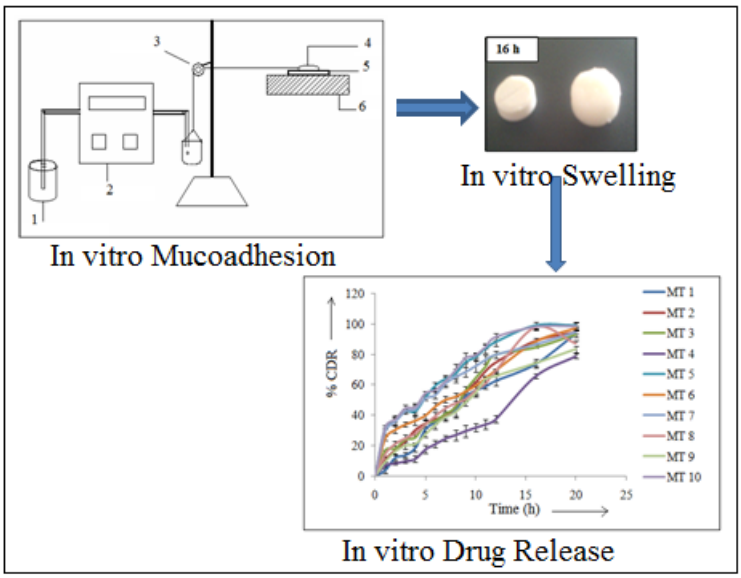

Graphical Abstract

most of patients. It act by binding to thyroid peroxidase and thereby inhibits the conversion of iodide to iodine. Thyroid peroxidase normally converts iodide to iodine (via hydrogen peroxide as a cofactor) and also catalyzes the incorporation of the resulting iodide molecule onto both the 3 and or 5 positions of the phenol rings of tyrosines found in thyroglobulin. Thyroglobulin is degraded to produce thyroxine (T4) and triiodothyronine (T3), which are the main hormones produced by the thyroid gland. Hence, methimazole effectively inhibits the production of new thyroid hormones.[17-20]

Thyrotoxicosis is the syndrome known as hyperthyroidism, arises as the body tissues have exposed to excessive levels of tri-iodothyronine (T_3) and thyroxine (T_4). In older adults, cardiac failure is another common problem consequence as the ageing heart works harder to deliver more blood and nutrients to the hyperactive body cells. The main causes are grave's disease, toxic nodular goiter and toxic edema. Graves' disease caused by production of antibodies in the blood that used to grow and secrete the thyroid hormone. Hence, it is necessary to maintain the thyroid harmones within levels because they play very important roles like regulation of basal metabolic rate (calorigenic action), growth of body organs, protein synthesis (anabolic action), regulation of cardiac output, myelination of CNS and also in GIT, reproductive and breast harmones, haemopoietic system, skin.[21]

The key issue of the methimazole is its dosing frequency of three times a day that decreases patient compliance, therapeutic efficiency, control of plasma drug levels and increases frequent dosing. There was no availability of SRDF of methimazole in market. Among different technologies used in sustained drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, FDA acceptance, and applicability to drugs with wide range of solubility. The most convenient way to achieve sustained release of active agent involves physical blending of drug with polymer matrix, followed by direct compression, compression molding, injection molding, extrusion, or solvent casting which results either in monolithic device or in swellable hydrogel matrix. Drug release from these systems is the consequence of controlled matrix hydration, followed by gel formation, textural/rheological behavior, matrix erosion and/or drug dissolution and diffusion, the significance of which depends on drug solubility, concentration, and changes in matrix characteristics.[22]

In the present investigation, an attempt has made to formulate the sustain release matrix tablets of methimazole using hydrophilic carbopol 934P in combination with hydrophobic ethyl cellulose and eudragit RL100. The different formulations were prepared and characterized by Fourier transform infra-red spectroscopy (FTIR), differential scanning colorimetry (DSC), *in vitro* mucoadhesion, *in vitro* swelling, erosion, *in vitro* drug release and stability studies. The novelty of this work is that, first time we attempted the SRDF of the methimazole because there was no availability of such system in the market. Swelling and subsequent erosion have been possible due to high viscosity polymer.

MATERIALS AND METHODS

Methimazole has obtained as gift sample from Innova Pharmaceuticals Pvt. Ltd. Nagpur. Carbopol 934P NF and ethyl cellulose were purchased from SD Fine Chemicals, (Bombay, India). PVP K30 was purchased from Loba Chemi-

Table 1: Compositions of different formulation batches of mucoadhesive matrix tablet

Ingradients (mg)	MT1	MT2	MT3	MT4	MT5	MT6	MT7	MT8	MT9	MT10
Methimazole	36	36	36	36	36	36	36	36	36	36
Carbopol 934P	60	60	75	75	90	90	90	105	105	120
Ethyl cellulose	60	75	75	90	60	75	90	75	60	60
Eudragit RL100	45	60	45	60	45	75	60	45	60	45
PVP K30	18	18	18	18	18	18	18	18	18	18
Lactose	78	48	48	18	48	03	03	18	18	18
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	300	300	300	300	300	300	300	300	300	300

cals (Bombay, India). Eudragit RL100 was obtained from Evonik Industries AG, Germany. All the reagents were of analytical grade and used without further purification.

Determination of sustained release dose for methimazole

The total dose of methimazole for once-daily sustained release formulation was calculated by using available pharmacokinetic data[23] in fallowing equation

$$Dt = Dose\,[1 + (0.693 * t)/t1/2)]$$

Where,

Dt indicates total dose of drug for sustained release, Dose is the immediate release part (9 mg), t indicates time during which sustained release is desired i.e. 24 h, and $t_{1/2}$ = half life of the drug.

$$Dt = 9\,[1 + (0.693 * 24)/5.5] \approx 36.0 \text{ mg.}$$

Preparation of tablets

The swelling matrix tablets of methimazole were prepared by direct compression method and their composition are shown in Table 1. PVP K30 has used as dry binder. Talc and magnesium stearate was used as lubricants. Drug, polymers and binder were mixed using a glass mortar and pestle for about 10 min passed through sieve no. 30 (Nominal mesh aperture size 500 µm). Then magnesium stearate was added as the lubricant and was passed through sieve no. 44 (Nominal mesh aperture size 355 µm) and thoroughly mixed for 2 min. The homogeneous powder mixture was fed through hopper and compressed in to 10 station tablet machine (Rimek mini-press-1, Mumbai, India) equiped with flat faced die-punch set of 9 mm diameter tooling (Stainless steel 314 grade).

FTIR studies

The physical mixtures were prepared by blending the samples with potassium bromide (1:100) and scanned over range of 4000-400 cm^{-1}. The infrared absorption spectra of pure methimazole and with carbopol, ethyl cellulose, eudragit (equal Ratio) and formulation batch MT 6 were analyzed using FTIR spectrophotometer (8400 S Shimadzu, Japan).

DSC studies

DSC examination was conducted for the pure methimazole and with carbopol, ethyl cellulose, eudragit and formulation batch MT 6 (Mettler Toledo DSC 822c, Switzerland). The thermograms were obtained at scanning rate of 10°C/min over a temperature range of 40 to 300°C under an inert atmosphere purged with nitrogen at a rate of 30 mL/min.

Physical testing

Weight variation test (Single pan electronic balance, AUX-120, Shimadzu, Japan), thickness and diameter measurements (Vernier Digimatic caliper, CD-6 CSX Mitutoyo Corporation, Japan) and hardness test (Pfizer type hardness tester, Besto, Mumbai, India) was done by the usual methods.(Hixson *et al*, 1931 Korsmeyer *et al*, 1983; Mooney *et al*,1981).

Drug content

Thirty tablets from each batch were weighed and powdered. The powder equivalent to the 300 mg of tablet was accurately weighed and dissolved in 70 mL of distilled water for 15 min, diluted to 100 mL with distilled water and filtered through the 0.45 µm filters (Nylon 66, Millipore, NY 11). 10 mL of filtrate was diluted to 100 mL of distilled water. Further dilution was made from 10 to 100 mL with the distilled water. Content of methimazole was determined spectrophotometrically by measuring the absorbance at 252 nm (UV-1700, Shimadzu, Japan).

Mucoadhesion studies

A simple apparatus has used to measure the minimum detachment force shown in (Figure 1). A piece of goat

stomach (2.0×1.0 cm) removed from newly sacrificed goat (Slaughter house) was adhered to a piece of glass, which was fixed on a plank and the plank was assembled with a little crown block. After hydrating the goat intestine with distilled water, the tablet was brought into contact with the goat intestine mucosa by applying little force for minute. After the initial contact, the tablet was encircled by a thread which fastened a light plastic beaker through the crown block. Then, water was flowed into the beaker at a speed of 3.0 mL/min using peristaltic pump until the tablet and goat intestine mucosa were pulled apart by the gravity of water. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The experiments were performed in triplicate and average values with standard deviation have been given.[24]

Ex vivo tablet adhesion retention period

In this an agar plate (1%, w/w) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 50 µl of 0.1 N HCl and attached to the center of agar plate by applying a light force with a finger tip for 20 sec. After five minutes, the agar plate was attached to a USP disintegration test apparatus (Electro lab disintegration tester. USP) and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5°C for 3 h. The adhering tablet on the plate was immersed into the solution at the lowest point and got out of the solution at the highest point. The retention period of the tablet on the plate was noted optically.

In vitro swelling studies

The ability of each tablet to swell in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) media was determined by swelling them up to its equilibrium. The measurement of swelling rates of carbopol matrix tablets was carried after immersion of tablet in the test medium to relate the observed phenomena of drug release with rate of polymer hydration. Weighed tablets (W_0) were placed in the closed plastic containers and rotated at 150 rpm using environmental orbital shaking incubator (Remi Instruments Ltd, Mumbai, India) with a medium of 0.1 N HCL (pH=1.2 and pH=6.8) at 37 ± 0.5°C. After 2, 5, 10, 20 min, and 1, 1.5, 2, 2.5, 3, 4, 6 ,8 and 16 h each swollen tablet was withdrawn from the medium and blotted to remove the surface water and then weighed (W_1) on an single pan balance. The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. Percent swelling due to absorbed liquid or water uptake was calculated by equation:

$$\text{Percent swelling} = \frac{W1 - W0}{W0} * 100$$

Where, W_0 indicates weight of the dry tablet before immersion into the test medium and W_1 indicates weight of the swollen tablet after immersion into the test medium.[23]

Erosion studies

The erosion of tablets was carried out after immersion of tablet in the test medium 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) media to relate the observed phenomena of loss on drying after equilibrium. Weighed tablets (W_0) were placed in the closed plastic containers and rotated at 150 rpm using environmental orbital shaking incubator with a medium of 0.1 N HCl (pH=1.2 and pH=6.8) at 37 ± 0.5°C. The swollen tablets were placed in hot air oven for the period of 24 h at 80°C. The wet samples were then dried in oven, allowed cooling in desiccators and finally weighed until constant weight was achieved (W_2). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point.

Percent erosion was calculated by equation,

$$\text{Percent erosion} = \frac{W0 - W2}{W0} \times 100$$

Where, W_0 indicates weight of the dry tablet before immersion into the test medium and W_2 indicates weight of swollen tablet after keeping into oven for 24 h at 80°C.[23]

In vitro drug release studies

In vitro drug release studies of the prepared matrix tablets was carried for a period of 24 h maintained at 37°C ± 0.5°C at 75 ± 1 rpm using an eight station USP XXII type 2 apparatus (Electrolab, Bombay, India). The agitation speed was 75 ± 1 rpm. The dissolution medium used in each flask was 600 ml of 0.1N HCl (pH 1.2) for initial 2 h, after that the dissolution media was changed to 6.8 (or pH was raised by addition of 300 ml of solution of tribasic sodium orthophosphate to each flask (15.2 g in water). The dissolution studies was carried out for 24 h (initial 2 h in pH 1.2 and rest in pH 6.8) under sink condition. At every 1 h interval samples of 5 ml were withdrawn from the dissolution medium and the volume was maintained with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 252 nm by UV spectrophotometer. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard.[25]

Stability studies

The optimized methimazole formulations were strip packed (Al–Al strip, 0.04 mm) and subjected to accelerated stability studies as per ICH Q1C guidelines (40°C

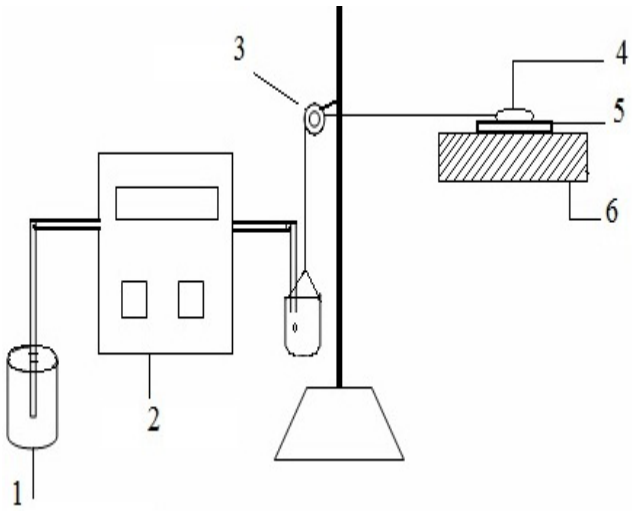

Figure 1: Laboratory developed assembly for mucoadhesion studies (1-Beaker filled with water, 2-Peristaltic pump, 3-Crown block, 4-Tablet, 5-Glass slide attached with goat stomach mucosa and 6-Plank)

± 2°C / 75% RH ± 5% RH). The samples were withdrawn periodically (0, 15, 30, 60, 90, and 180 days) and evaluated for the different physicochemical parameters such as appearance, weight variation, thickness, hardness, drug content, and *in vitro* release studies.

RESULTS

FT-IR studies

The FT-IR spectra of pure drug, physical mixture of polymer, physical mixture of drug and polymers and optimized formulation batch MT6 are shown in figure 2. Spectra of drug showed the respective functional group at NH-3158.54 cm^{-1}, aromatic CH-3014.84 cm^{-1}, aliphatic CH 2899.11 cm^{-1}, NH-1573.97 cm^{-1}. There was no significant change in peak intensity of pure drug and drug in the optimized swelling matrix tablets.

DSC studies

DSC thermogram of pure methamizole, carbopol 934, ethyl cellulose, eudragit RL100 and optimized swelling matrix tablets MT6 are shown in figure 3. The thermal curve of pure methimazole exhibited sharp endotherm at 143.40°C and peak at 144.82°C. Thermal curve of mixture showed the endotherm at 144.09°C and peak at 145.97°C which is in melting range of methimazole (143-147°C). There was no change in the melting point of pure drug and drug in the optimized swelling matrix tablets MT6.

Physicochemical properties of carbopol based swelling matrix tablets

The thickness, hardness, friability, weight variation, drug content and mucoadhesive force of the different formulation of the swelling matrix tablets are given in Table 2. The optimized batch MT 6 has a thickness of 3.37 ± 0.11 mm. Percent friability of different batches were found to be in range of 0.215 ± 0.003 to 0.290 ±0.170 %. The weight variation was 298.08 ± 0.40 g meet the USP requirements for weight variation tolerance. The hardness of different formulations was found to be in the range of 5.23 ± 0.68 kg/cm^2 to 7.23 ± 0.81 kg/cm^2. The drug content of tablets was found to be (98.63 ± 0.90) in between 94 to 106%.

Mucoadhesion studies

Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a poten-

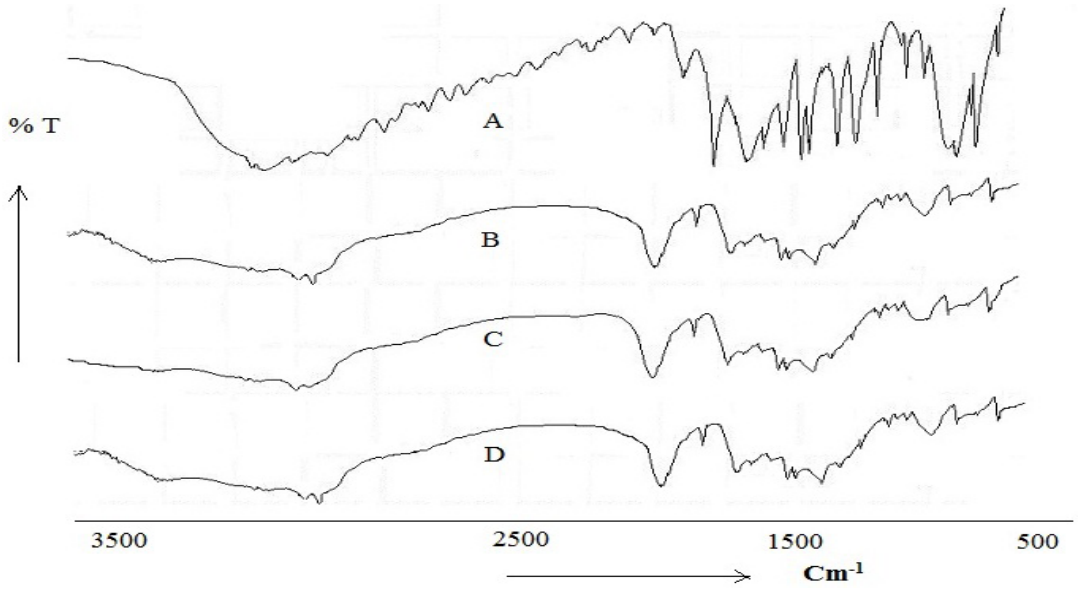

Figure 2: FT-IR spectra of (A) Pure methamizole, (B) Methamizole: carbopol: ethyl cellulose: eudragit RL 100, (C) Carbopol: ethyl cellulose: eudragit RL 100 (D) Optimized formulation batch MT6

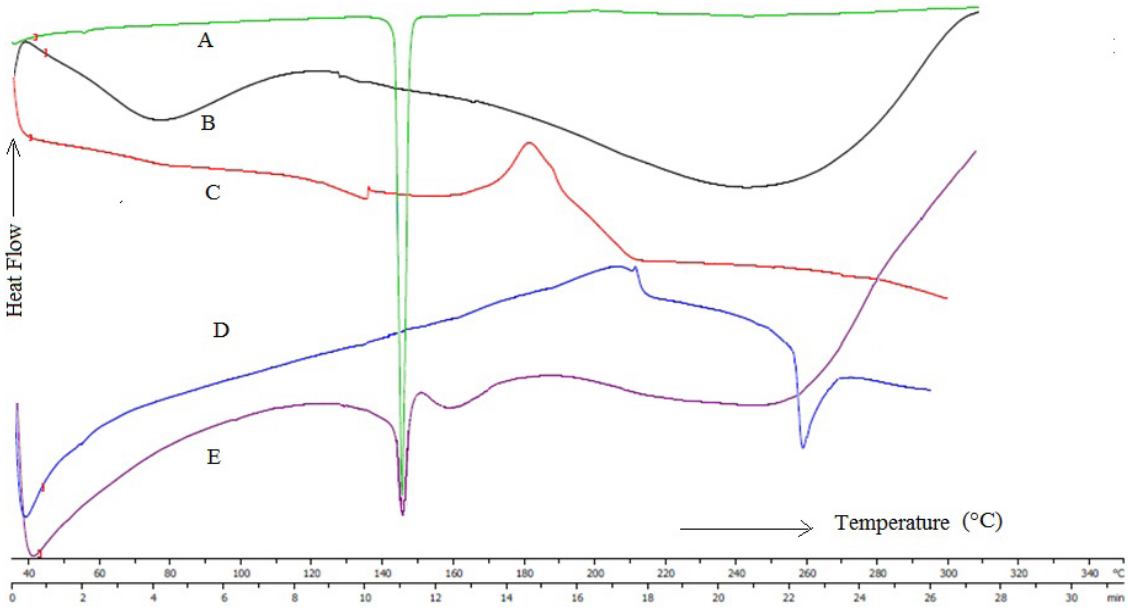

Figure 3: DSC thermogram of (A) Pure methamizole (B) Carbopol 934 (C) Ethyl cellulose (D) eudragit RL100 and (E) Optimized swelling matrix tablets MT6

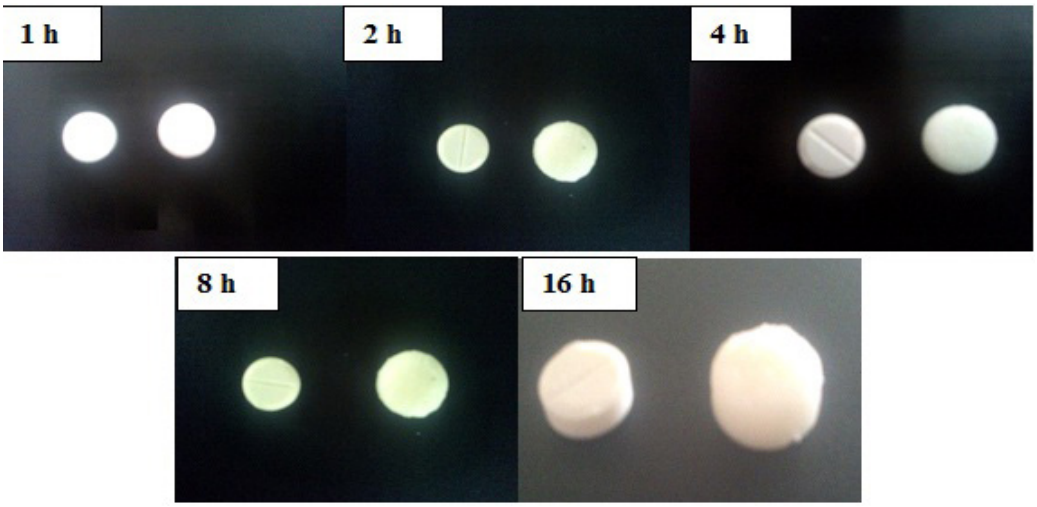

Figure 4: Swelling behavior of methimazole matrix tablet after 1 h, 2 h, 4 h, 8 h, and 16 h

tial means of extending the drug release from delivery system. It was found that, the optimum concentration of polymer carbopol 934P, ethyl cellulose and Eudragit RL 100 in formulation code MT6 showed the best mucoadhesive force. The optimized swelling matrix tablet had the mucoadhesive force about 14.813 ± 0.085 N.

Ex vivo tablet adhesion retention time

Tablet adhesion retention time test revealed good *in vitro* mucoadhesive ability of matrix tablets. The optimized formulation code MT 6 had maximum adhesion retention time about 11.16 ± 0.10 h.

Swelling studies

The results obtained of swelling studies are shown in the Figure 4. The proposed mechanism of swelling was the polymer absorbs water and swells as the water penetrates further into the device. The swelling behavior indicated a rate at which tablet absorbed water from test media and swelled. The changes in weight, characteristic of water uptake and swelling started slightly from beginning until the 16 h of experiment. Optical observations indicated that the matrices appeared to swell slowly from the beginning showed the images of swollen matrix tablets during swelling study. The surface of tablet gradually swelled with core remaining intact hence the tablet swelled efficiently and formed a soft gel with some erosion. Percent swelling of tablets and it is confirmed that, the initially less swollen tablet pass through the pylorus during gastiric emptying within 2-3 h. It was found that the batch MT 6 have maximum swelling up to 60 %, which is slightly increased right at 16 h.

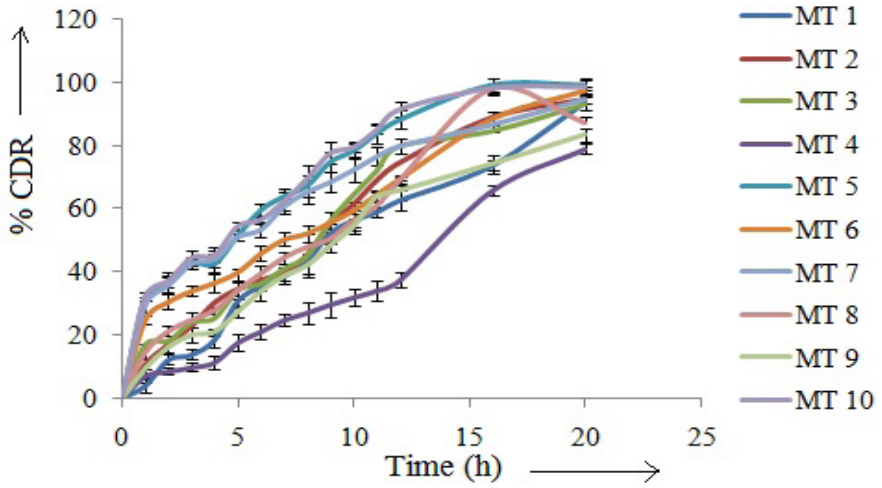

Figure 5: Percent cumulative drug release of mucoadhesive matrix tablets batch MT 1 to MT10

Table 2: Physicochemical properties of various formulation batches of matrix tablets

Batch Code	Hardness (Kg/Cm²)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug Content (%)	Mucoadhesive Force (N)
MT1	5.23 ± 0.68	3.36 ± 0.07	0.24 ± 0.03	298.66 ± 2.39	97.45 ± 0.71	8.16 ± 0.05
MT2	6.10 ± 0.45	3.36 ± 0.11	0.21 ± 0.11	298.25 ± 2.45	98.23 ± 0.80	8.33 ± 0.02
MT3	6.52 ± 0.51	3.33 ± 0.05	0.25 ± 0.19	297.56 ± 1.77	98.75 ± 0.40	10.41 ± 0.11
MT4	5.82 ± 0.14	3.24 ± 0.07	0.28±0.26	298.23 ± 2.09	98.32 ± 0.63	10.82 ± 0.09
MT5	6.69 ± 0.22	3.26 ± 0.09	0.27 ± 0.03	299.36 ± 2.81	97.55 ± 0.75	14.45 ± 0.08
MT6	6.40 ± 0.21	3.37 ± 0.11	0.25 ± 0.17	298.08 ± 2.0	98.43 ± 0.20	14.81 ±0.85
MT7	6.87 ± 0.18	3.35 ± 0.13	0.22 ± 0.06	297.57 ± 1.8	98.85 ± 0.60	14.36 ± 0.02
MT8	7.23 ± 0.81	3.32 ± 0.11	0.26 ± 0.13	299.26 ± 1.9	97.25 ± 0.51	14.95 ± 0.10
MT9	7.19 ± 0.47	3.28 ± 0.09	0.29 ± 0.17	298.04 ± 1.7	98.23 ± 0.13	15.15 ± 0.10
MT10	7.22 ± 0.49	3.35 ± 0.15	0.27 ± 0.16	297.37 ± 1.8	98.23 ± 0.30	15.71 ± 0.14

Table 3: *In vitro* drug release kinetics of the different batches of sustained release matrix tablets

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer-Peppa's (R^2)	Korsmeyer-Peppa's (n)
MT1	0.9821	0.9532	0.9522	0.9712	0.4223
MT2	0.9274	0.9245	0.9537	0.9245	0.4975
MT3	0.9214	0.9540	0.9321	0.9712	0.7236
MT4	0.9247	0.9524	0.9211	0.9242	0.6941
MT5	0.9521	0.9251	0.9541	0.9823	0.7513
MT6	0.9214	0.9214	0.9524	0.9415	0.5928
MT7	0.9642	0.9632	0.9441	0.9412	0.6027
MT8	0.9551	0.9214	0.9255	0.9321	0.7924
MT9	0.9581	0.9227	0.9243	0.9213	0.7045
MT10	0.9924	0.9844	0.9690	0.9827	0.4721

Erosion studies

Drug release was by both the mechanism that diffusion and erosion. Matrix tablet also studied for its erosion and it is confirmed that till 16 h, 53.08 ± 3.44 erosion (mass loss) matrix tablets took place. After swelling and drug release, percent erosion was increased. Due to increase in percent erosion and drug release, the size of system was reduced.

In vitro dissolution studies of matrix sustained release tablets

Swelling matrix tablets of formulation code MT6 had 98.31 % drug release for 20 h. According to the theo-

retical release pattern, calculation showed SRDF should drug release nearly about 100 percent for 24 h (Figure 5). This approach involves the use of swelling polymers that could retard the drug release for the period of 20 h in the gastrointestinal tract.

Drug release kinetics of dissolution data

To know the mechanism of drug release from these formulations, the data was treated according to Zero order (% cumulative drug release vs time), First order approximation (log cumulative percent drug remaining to be diffused vs. time), Higuchi's approximation (cumulative percent drug diffused vs. square root of time), Korsmeyer-Peppas approximation (log cumulative percent drug diffused vs. log time).

The release exponent (n) was calculated from the slope of the appropriate plots, and the regression coefficient (R^2). The *in vitro* release patterns of the drug from the formulations shows regression coefficient (Higuchi's kinetics) R^2=0.9690 (Table 3). Korsmeyer-Peppa's kinetics showed the 'n' value of 0.47 found to be in between 0.45 and 0.89 indicates that diffusion is coupled with erosion and hence this mechanism is called anomalous diffusion and zero order kinetics as it indicated that the tablets were swollen and the drug release was controlled by swelling.[24,25]

Stability studies

After the 3 month time interval, when the optimized batch (MT 6) was subjected for organoleptic properties, appearance, friability, remains unaffected. The hardness, drug content and drug release were found to be 6.42 ± 0.05 kg/cm^2, 98.72 ± 0.68 and 98.32 ± 1.4 %, respectively.

DISCUSSION

On the basis of *in vitro* swelling, *in vitro* mucoadhesion, *ex-vivo* adhesion retention time and *in vitro* drug release, the formulation batch MT6 was selected as the optimized swelling matrix tablet.

To study the compatibility issue of drug with excipients, we used the FTIR and DSC measurements. It was observed that there was no significant change in peaks of FTIR spectra during compatibility studies. The spectra of physical mixture indicated that, the stable nature of the drug. Therefore, it is revealed that all the ingredients are compatible with each other. According to the DSC findings of the matrix tablet, no major thermal event corresponding to chemical interaction was observed. Hence, it is confirmed the suitability of each excipients with drug to prepare inert matrices.

Tablet adhesion retention period test revealed *ex vivo* mucoadhesive ability of matrix tablets. This might be contains large numbers of negatively charged carboxyl and sulfate groups these are responsible for adhesion of tablet to the mucus membrane. The optimized batch MT6 had adhesion retention time about 11.16 ± 0.10 h.

To control the release of highly water soluble drug from hydrophilic matrix it was obvious to use the hydrophobic material in combination. Use of single polymer may control the release rate but we tried the use of two hydrophobic polymers to ease the more prolong release rate of drug. The *in-vitro* release for matrix tablets from the formulation code MT 1 to MT 10 showed much slower release rate because low water affinity for ethyl cellulose and eudragit (RL 100). The release rate of drug was decreased when proportion of polymer was increased but differed quantitatively in different drugs and different matrix materials (Shlieout *et al*, 1996; Siepman *et al*, 2001). As relative concentration of ethyl cellulose and Eudragit is increased in the tablet, retards the penetration of dissolution medium in matrix by providing more hydrophobic environment. This causes delay in the release of the drug from the tablet. At lower concentration initial burst effect observed, while at higher concentration much slower release rates took place. Carbopol 934P along with eudragit RL 100 and ethyl cellulose was found to be excipients of controlling the release rate of methimazole in matrix tablets for 20 h.

Methimazole release pattern was decreased with increase in carbopol 934P content and viscosity/molecular weight. According to Siepman and Peppas suggested that drug release from matrices is sequently governed as steep water concentration gradient is formed at the polymer/water interface resulting in water imbibition into the matrix. Due to imbibitions of water, polymer swells resulting change in polymer and drug concentration and increasing dimension of system. Upon contact with water drug dissolves and diffuses out of the matrix due to concentration gradients with increasing water content, the diffusion coefficient of the drug increases substantially. Thus, carbopol 934P was found to be dominating excipient controlling the release rate of methimazole in matrix tablets.

After swelling and drug release of system, percent erosion was increased. Due to increase in percent erosion and complete drug release the size of system was reduced to some extent. The optimized formulations (MT 6) had shown the drug release up to 20 h hence these formulations revealed as SRDF. Therefore, the major problem associated with drug that its high solubility, dosing frequency of three times a day could solve the problem and it's necessary for better patient compliance.

The release of the drug from a matrix tablet containing hydrophilic polymers generally it involves factor of

diffusion. Diffusion is related to the transport of drug from the dosage matrix into the *in vitro* studies fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases.

Stability studies were performed as per ICH 1C guidelines. Physicochemical parameters were determined at the interval of 30, 60 and 90 days It was found that the optimized tablets of batch MT 6 was stable even at exaggerated condition of temperature and humidity. For further confirmation it will requires the *in vivo* studies in animals or healthy volunteers and *in vitro in vivo* correlation.

CONCLUSION

In the current work, a carbopol 934P based mucoadhesive matrix tablet containing a low dose of highly soluble methimazole is described. The formulation batch MT6 was found to be optimized batch which exhibited the drug release up to 98.34 % for 20 h. Percent swelling and mucoadhesive force of formulation MT6 were found to be 60 and 14.813 ± 0.085 N, respectively. The optimized matrix tablets had *ex vivo* adhesion retention time of 11.16 ± 0.10 which deliver the drug at particular region in the gastrointestinal region. It can be concluded that, carbopol 934P with Eudragit RL 100 and ethyl cellulose at optimum proportions offers promising potential for SRDF of highly soluble drugs.

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Highlights of Paper

- We prepared the matrix tablets by direct compression technique.
- We performed mucoadhesion studies by two different methods.
- Carbopol 934P along with eudragit RL 100 and ethyl cellulose was found to be excipients of controlling the release rate of methimazole in matrix tablets for 20 h.
- We successfully developed the sustained release dosage form of the highly soluble methimazole.

Author Profile

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