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Dixit Ashish
Professor, Spectrum Hi Pharmacy College, Sultanpur (U.P)

Sahani Vibhu
Professor, LLRM Medical College Meerut (U.P)

Correspondence

Dr. Dixit Ashish
Professor, Spectrum Hi Pharmacy College, Sultanpur (U.P)

Email: ashdixit2000@gmail.com

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Formulation and Evaluation of Floating Tablet of Thiocolchicoside

Dixit Ashish and Sahani Vibhu

ABSTRACT

Thiocolchicoside is a centrally acting analgesic and is used to treat moderate to severe pain. Thiocolchicoside is rapidly and almost completely absorbed after oral administration, showing good bioavailability. Hence the main objective of the work was to design, development and *in vitro* evaluation of natural gum based matrix tablet of Thiocolchicoside.

All the batches were evaluated for angle of repose, carr's index, hausner's ratio, hardness, thickness, weight variation, drug content and *in vitro* release characteristics. The results of DSC and IR spectroscopy exhibited that no chemical interaction between drug and polymers and no shifting in the IR peaks was observed.

The release kinetics and the mechanism of drug release by regression coefficient analysis were investigated. The optimized tablets having HPMC provided more sustained drug release than other polymers. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Key words: Thiocolchicoside , HPMC K15M, Carbopol 934P, MCC PH102.

1. INTRODUCTION

1.1 Floating Drug Delivery Systems

The goal of any drug-delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. That is the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

1.1.1 Advantages of Floating drug delivery system

1. The gastro-retensive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
2. Improves patient compliance by decreasing dosing frequency.
3. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
4. Better therapeutic effect of short half-life drugs can be achieved.
5. Gastric retention time is increased because of buoyancy.
6. Drug releases in controlled manner for prolonged period

1.1.2 Disadvantages of Floating Drug Delivery System

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
3. The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system causes irritation to gastric mucosa.

1.2 Classification of Floating Systems

1.2.1 **Non-effervescent systems**
Single unit
Multiple units

1.2.2 **Effervescent systems**
Single unit
Multiple units

1.2.1 Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, C02 is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

1.2.2 Non-effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene.

The formulation method includes a simple approach of throughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1.

1.3 Controlled Drug Delivery Systems

The goal of any drug-delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. That is the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

1.3.1 Classification of controlled release system

1.3.1.1 Delayed release

A delayed release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

1.3.1.2 Sustained release system

The goal of sustained drug delivery are to conserve and maintain effective drug concentration, eliminate night time dosage, improve compliance and decrease side effects thus, optimizing drug therapy.

1.4 Methods Used To Achieve Sustained

1.4.1 Diffusion systems

In these systems, the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices:

1.4.1.1 Reservoir devices
1.4.1.2 Matrix devices

1.4.1.1 Reservoir devices

This is a device in which core of drug is surrounded by a polymeric membrane. The release of drug from a reservoir device is governed by fick's first law of diffusion. The common methods used to develop reservoir type devices include microencapsulation of drug particles and press-coating of tablets containing drug cores.

1.4.1.2 Matrix devices

These are devices in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix. The rate of release of drug dispersed as a solid in an inert matrix has been described by higuchi.

1.5 Dissolution systems

A drug with a slow dissolution rate will yield an inherently sustained blood level. In principle, then, it would seem possible to prepare controlled release products by controlling the dissolution rate of drugs that are highly water soluble. This can be achieved by preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material, or by incorporation it into a tablet with a slowly soluble carrier. Ideally surface area available for dissolution must remain constant to achieve a constant release rate. Most of the products fall in to two categories encapsulated dissolution systems and matrix dissolution systems.

1.6 Matrix system

To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following parameters must be considered:

- The chemical nature of support (generally, the support are formed by polymeric network)
- The physical state of drug (dispersed under molecular or particulate form or both)
- The matrix shape and alteration in volume as a function of time
- The route of administration (oral administration remains the most widely used but other routes are adaptable.

1.6.1 Classification of matrix system

1.6.1.1 Mineral matrix

- Drug retained in the support
- Drug adsorbed on the support

1.6.1.2 Lipidic matrix

- Deliver by diffusion
- Deliver by surface erosion

1.6.1.3 Hydrophilic matrix

- Un-limited swelling, deliver by diffusion
- Limited swelling controlled delivery through swelling

1.6.1.4 Inert matrix

- Controlled delivery by diffusion

1.6.1.5 Biodegradable matrix

- Non-lipidic

2. FORMULATION, DEVELOPMENT AND STANDARDIZATION OF DRUG

2.1 Determination of Wavelength (Λ_{max})

An amount of 1 mg of Thiocolchicoside was individually weighed and dissolved in 100 ml of phosphate buffer solution of pH 7.4 to obtained final strength 1µg/ml and scan in a range of 220-440 nm in basic spectrum mode and the ultraviolet absorption λmax of Thiocolchicoside is recorded and compare with reported literature value.

2.2 Preparation of Calibration Curve of Thiocolchicoside

The standard curve of Thiocolchicoside was prepared in phosphate buffer (pH7.4). Accurately weighed 1 mg of Thiocolchicoside was dissolved in 100 ml of phosphate buffer (pH 7.4) to give a concentration of 0.01 mg/ml. Further from the solution, 0.5ml, 1.0ml, 1.5ml, 2.0ml, 2.5ml and 3.0 ml were taken in separate 10ml volumetric flask and diluted up to 10ml with the help of phosphate buffer (pH=7.4) to produce 5µg/ml, 10 µg /ml, 15µg /ml, 20µg /ml, 25µg /ml and 30µg /ml

2.3 Preparation of Matrix Tablets of Thiocolchicoside

Matrix tablets containing 8mg of Thiocolchicoside along with various amounts of polymers such as HPMC and Carbopol, and other excipients (starch, lactose, citric acid, tartaric acid, magnesium stearate) were prepared by direct compression technique

Step 1: In the first step, active pharmaceutical ingredients and excipients weighed accurately and screened through a 60,100 & 200 -mesh sieve.

Step 2: Required materials except lubricant were dry mixing properly after this thiocolchicoside is mixed with exicipients.

Step 3: The granules were lubricated with magnesium stearate. Before compression, the surfaces of the die and punch were lubricated with talcum.

Step 4: The lubricated granules were compressed with a 16 station tablet machine.

2.4 Evaluation of Granules for Matrix Tablet

2.4.1 Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 1.5 gm of powder from each formula was introduced in a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall onto a hard surface from a height of 2.5 cm at 2 sec intervals. The tapping was continued till no volume change was noted. LBD and TBD were determined by following formula:

Calculation of low bulk density (LBD)

LBD = weight of powder / volume of packing

Calculation of tapped bulk density (TBD)

TBD = weight of powder / tapped volume of packing

2.4.2 Compressibility Index (CI)

Compressibility index is important measure that can be measure from the bulk and tapped density. The compressibility index is obtained from below mention formula:

Calculation of compressibility index

$CI = 100 (Vo – Vf)/ Vo$

Where, *Vo*: Initial volume , *Vf* : Final volume

2.4.3 Hausner's ratio (HR)

It indicates the flow properties of the powder and measure by the ratio tapped and bulk density using the formula:

Calculation of hausner ratio

Hausner ratio = Tapped density/Bulk density

2.4.4 Angle of repose

The angle of repose of the powder was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder then allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated by using the following equation

Calculation of angle of repose

$\tan = (h/r)$

Where, *h:* height of the powder cone
R: radius of the powder cone

2.5 Evaluation of Compressed Tablet

2.5.1 Thickness

The thickness of the tablets was determined using vernier caliper. Five tablets from each batch were used and average values were calculated.

2.5.2 Weight Variation

To study weight variation, 20 tablets of each formulation were weighed using an electric balance, and the test was performed according to official method.

Calculation of percentage weight deviation

% deviation=(Individual weight – Average weight)/Average weight × 100

2.5.3 Hardness

For each formulation, the hardness of 3 tablets was determined by using monsanto hardness tester.

2.5.4 Friability

The test is performed in Roche friabilator. 20 tablets were weighed accurately, after dedusting them carefully tablets were placed in the drum and rotated it for 100 times. The tablets were removed, dedusted them again and weighed accurately. A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 percent is acceptable for most tablets. This process was repeated for all batches and the percentage friability was calculated by following formula:

Calculation of percentage friability

$\% F = \{1- (Wt/W)\} \times 100$

Where, *% F:* friability in percentage

W: Initial weight of tablet ,

Wt: weight of tablet after revolution

2.6 Drug Content of Thiocolchicoside

Accurately weighed 50 mg of Thiocolchicoside reference standard into a 50.0 ml volumetric flask, dissolve in methanol and dilute to volume. Accurately weighed 50 mg of Thiocolchicoside and added into a 50.0 ml volumetric flask. Volume makeup was done by methanol. One night complete stirring was allowed to dissolve drug into solvent. Solution was extracted, filtered with nylon filter paper and analysed at λmax of 220-440 (370) nm with help of UV spectrophotometer.

2.7 In vitro Buoyancy / Floating Study

In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 200ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time(TFT).

2.8 Swelling Index

Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium.These eventually influences the release, slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 8 hours. The percentage weight gain by the tablet was calculated by using the formula

Swelling index (S.I) ={(Wt-Wo)/Wo}x 100

Where, S.I. = swelling index
Wt = Weight of tablet at time t
Wo = Weight of tablet before immersion

2.9 *In vitro* Drug Release Studies

2. 10 Dissolution parameters

Medium: 0.01N hydrochloride (1st two hours only), phosphate buffer (pH= 7.4)

Type: USP apparatus II (Paddle) type
RPM : 100
Quantity : 900 ml
Temperature : 37± 0.5°C
Duration : 10 hours
Sampling time : 1st hr, 2nd hr, 3rd hr, 4th hr, 5 th hr, 6th hr, 7 th hr, 8 th hr, 9 th hr and 10 th hr.

2.11 Preparation of Buffers Solution (I.P. 1996)

2.11.1 Preparation of 0.01N hydrochloride

0.85ml of concentrated hydrochloric acid was accurately measured and diluted to 1000 ml with distilled water to obtain 0.01N hydrochloride.

2.11.2 Preparation of 0.2M monobasic potassium phosphate

About 27.218gm of monobasic potassium phosphate (KH2PO4) was dissolved and diluted to 1000 ml with distilled water.

2.11.3 Preparation of 0.2M sodium hydroxide solution

About 8.0gm of sodium hydroxide (NaOH) was dissolved and diluted to 1000ml with distilled water

2.11.4 Preparation of phosphate buffer (pH = 7.4)

250 ml of mono basic potassium phosphate (KH2PO4) was placed in a 1000ml volumetric flask, 195.5 ml of 0.2M NaOH was added and volume was made up to 1000ml with dematerialized water and pH adjusted to 7.4 using dilute NaOH solution. The buffers and reagents were prepared for different volumes depending on the analysis requirements based on the above USP specified standard preparation procedures.

2.12 *In vitro* dissolution study

In vitro drug release study for the prepared matrix tablets were conducted for a period of 10 hours using a 6 station USP TDL-06L apparatus at temperature 37±0.5 oC and at 100 rpm speed. Initially the dissolution was carried out in 500ml of 0.1N hydrochloride, pH 1.2 for 2 hours and then in 900ml phosphate buffer pH 7.4 up to 10 hours. At every one hour interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 370 nm for Thiocolchicoside by using a UV-Visible spectrophotometer. The amount of drug present in the samples was calculated. Commercial sustained release (CSR) tablet: Thiospas ® (Thiocolchicoside 8 mg) was purchased from the market and was evaluated for *in vitro* release characteristics by using the above procedure.

2.13 Drug Analysis

Thiocolchicoside was analyzed by UV spectrophotometer at 254nm. Calibration curve was prepared in phosphate buffer of pH 7.4 in concentration ranges from 5-30µg/ml. Correlation coefficients was found to be (r2=0.9980) in all cases and hence indicates that the drug is in pure form.

2.14 Calibration Curve of Thiocolchicoside

The calibration curve was prepared by using absorbance data of Thiocolchicoside at λmax254 nm in phosphate buffer of pH 7.

$$CI = \frac{pt - pb}{pt}$$

Table 1.Standard calibration curve for Thiocolchicosidein phosphate buffer (pH7.4)

S.No.	Conc.(µg/ml)	Absorbance at
1	0	00±0.000
2	5	0.043±0.006
3	1	0.074±0.001
4	1	0.112±0.006
5	2	0.148±0.006
6	2	0.180±0.001
		0.214±0.001

Table 2. Optical characteristic and precision

Optical characteristic	Range
λmax (nm)	**254**
Correlation coefficient (r2)	**0.9980**
Slope (a)	**0.007**
Intercept (b)	**0.004**
Regression equation (y)	**0.007(x)+0.004**

3. PREFORMULATION STUDIES

3.1 FTIR Spectroscopy

The IR spectra of pure drug Thiocolchicoside and optimized formulation have been showed in figure 3.3 and 3.10 respectively. The major peaks observed in the spectra for tablet formulation were OH-stretching at 3650-3700 cm-1 , C-H stretching at 3400-3000 cm-1 (methoxy group), C-H stretching at 3000-2900cm-1 (methylgroup),C=ring stretch at 1500-1600 cm-1, C-N stretch at 1300-1250 cm-1,C-O-C asymmetric stretch at 1190-1160 cm-1, C-H bend at 790-750 cm-1, C=C bend at 700-690 cm-1, which are characteristics of Thiocolchicoside. When the IR spectra of pure dugs i.e. figure 3.3 is compared to IR spectra of physical mixture i.e. figure 3.4, it was found that there was no interaction found among them as well as it was also found that there was no variation in IR spectra of optimized product (F9) given figure.

Characteristic	Functio	Peak (cm^{-1})
C-N stretching	C-N group	1300-1250 cm^{-1}
C-H stretching	0CH_3 group	3400-3000cm^{-1}
C-H Stretching	CH_3 group	3000-2900 cm^{-1}
C=C bending	C=C in six member ring	700-690 cm^{-1}
=C-H out of plane bending	C=C aromatic	790-750 cm^{-1}
C=ring	C=ring	1500-1600 cm^{-1}
O-H stretching vibration,inter-molecular	Bonded with–OH	3650-3700 cm^{-1}

Table 3.3 Characteristics peaks for IR spectra

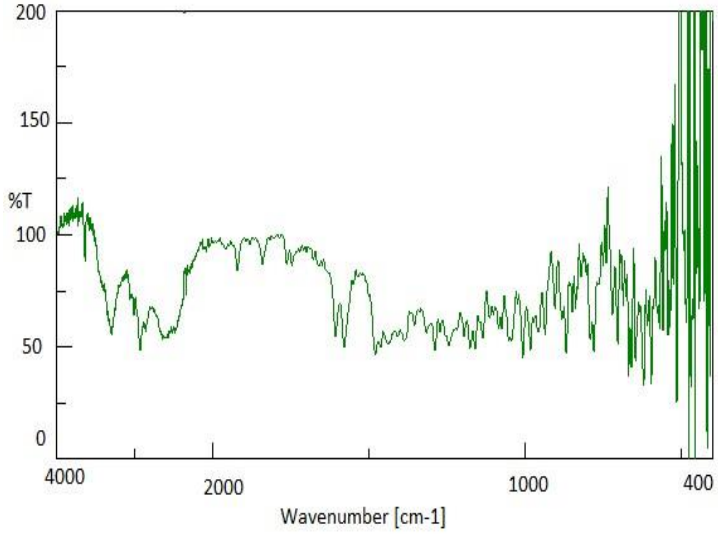

Figure 3.3 IR spectra of pure drug Thiocolchicoside

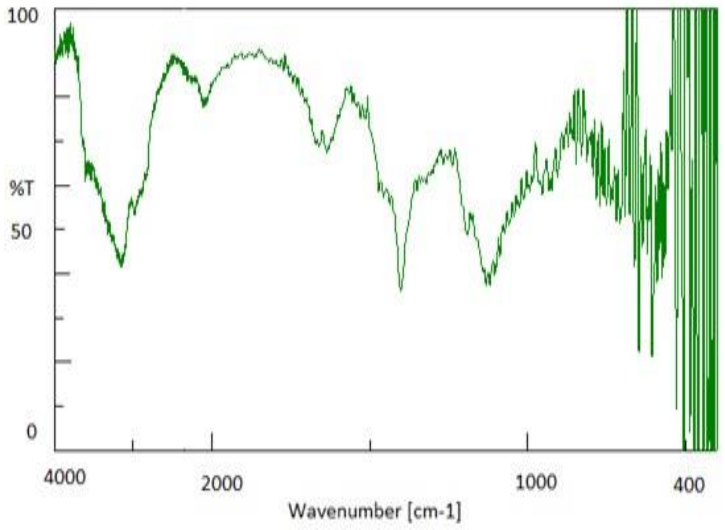

Figure 3.4 IR Spectra of HPMC15 Cps

3.2 Differential Scanning Calorimeter (DSC)

In order to confirm the physical state of the pure drug, DSC of the drug alone, physical mixture of drug and excipients was recorded. The DSC trace of drug showed a sharp endothermic peak at 182.21°C, its melting point. The physical mixture of drug and polymers showed the endothermic peak at 176.8°C as the individual component, indicating that there was no interaction between the drug and the polymer in the solid state

4. EVALUATION OF GRANULES FOR MATRIX TABLET

The physical mixture for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density and Carr's index (table 3.4). Angle of repose were found between 25 o -31o and Carr's index values were found between 12-18 % for the powder of all the batches indicating excellent to poor flow ability and compressibility. Hausner's ratio was found to bein the range of 1.14 to1.23 for all the batches indicating that passable and poor flow properties

5. SUMMARY & CONCLUSION

In the present work, an attempt was made to prepare of sustained release matrix tablets of Thiocolchicoside by direct compression method. The prepared matrix tablets containing Thiocolchicosid using different ratio of citric acid and carbopol was found to be good without any tablet defects i.e. sticking, chipping, capping.The results of DSC and IR spectroscopy exhibited that no chemical interaction between drug and polymers and no shifting in the IR peaks was observed. Before compression, the physical mixture of excipients i.e. granules were evaluated by considering the various parameters like angle of repose, bulk density, tapped density and carr's index.Citric acid and Carbopol were used as 10%, 15% and 20% (w/w) of total tablet weight with the combination of HPMC 15cps.Both gums with 20% concentration retarded the Thiocolchicoside release beyond 12 hr. Citric acid was found more effective than carbopol at low concentration (10%) with combination of HPMC 15cps in controlling the drug release rates. The formulation (F9) containing both gum at maximum concentration (each 20% w/w of citric acid and carbopol) with HPMC 15cps shows greater release retardant of drug from the matrix system. The kinetics of drug release was best explained by zero order equation and Korsmeyer Peppas model. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed. The values of *n* were in the range of 0.359 to 0.556 (i.e. more than 0.5, table 20) indicating non-Fickian release (diffusion controlled), which indicated drug release to occur through diffusion and relaxation. The effect of formulation variables on drug release was tested for significance level by using analysis of variance (ANOVA). Difference was considered significant when $p<0.05$. From the above study it was concluded that the prepared matrix tablets were revealed satisfactory characteristics and promising drug release. Thus, sustained release matrix tablets of Thiocolchicoside using natural gums were successfully formulated, evaluated and found to be suitable candidates in extending the release of the drug from the matrix tablets.

While the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called 'once-a- day' formulations may be replaced by novel gastroretentive products with release and absorption phases of approximately 24 hours.

The floating tablets would result in the increament of the solubility and other parameter for the increase in the bioavailability and the sustained and controlled release can be made by effective by the floating tablet methods. The articles would also result in the help of the conduct of the clinical trials study.

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Table3.4 Pre-compression evaluation matrix tablets of Thiocolchicoside

Formulation code	Angle of repose (^{0})*	Bulk density(gm/ml)*	Tapped density(gm/ml)*	Carr's	Hausner's
F1	25.79±0.15	0.241±0.010	0.285±0.05	17.52±0.07	1.22±0.03
F2	31.27±0.46	0.322±0.010	0.374±0.07	12.56±0.52	1.14±0.01
F3	26.91±0.33	0.283±0.00	0.352±0.08	18.05±0.71	1.21±0.02
F4	27.51±0.04	0.294±0.00	0.366±0.06	18.37±0.35	1.22±0.01
F5	25.36±0.18	0.296±0.00	0.362±0.01	15.14±0.25	1.19±0.03
F6	26.59±0.04	0.278±0.00	0.331±0.00	15.17±0.05	1.16±0.07
F7	29.11±0.13	0.292±0.00	0.344±0.09	16.43±0.25	1.17±0.05
F8	26.99±0.11	0.285±0.01	0.347±0.06	16.92±0.12	1.21±0.03
F9	28.41±0.16	0.289±0.00	0.338±0.06	16.09±0.03	1.23±0.04

***Values are expressed as mean ±SD (n=3)**

Table3.5 Characterization of prepared Thiocolchicoside matrix tablet (8 mg)

Formulation code	Wt. variation (mg)**	Hardness (kg/cm2)**	Friability (%) **	Thickness (mm)**	Buoyancy LagTime (Sec) *	Drug content (%)*
F1	2.410±0.32	1.86±0.030	0.746±0.015	2.713±0.030	40	100.4±0.50
F2	2.326±0.09	2.15±0.025	0.663±0.015	2.620±0.095	53	102.1±0.88
F3	2.350±0.21	2.80±0.050	0.786±0.030	2.893±0.025	61	101.1±0.90
F4	2.425±0.08	2.50±0.015	0.913±0.020	2.796±0.020	Fail	98.67±0.46
F5	2.480±0.13	2.80±0.015	0.676±0.015	2.870±0.020	55	99.48±0.42
F6	2.440±0.25	2.20±0.026	0.760±0.030	2.963±0.025	70	97.83±0.67
F7	2.391±0.18	2.34±0.019	0.666±0.013	2.810±0.019	38	100.7±0.52
F8	2.382±0.27	2.40±0.026	0.566±0.015	2.510±0.029	65	99.94±0.57
F9	2.376±0.13	2.80±0.025	0.466±0.016	2.486±0.030	82	98.78±0.38

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