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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MATRIX TABLET OF THIOCOLCHICOSIDE USING NATURAL POLYMER GUAR GUM

Dr.Vivek Jain1, Shrikant Patel*, Anwar Iqbal Khan
NRI Institute of Pharmacy, Bhopal, Madhya Pradesh, India

Abstract-Matrix tablets are the kind of tablet which is aimed such that it releases its substances regarding first order kinetics or zero order kinetics due to distinctive procedure. The study was begun with the drug analysis and preparation of calibration on a UV-Visible spectrophotometer in phosphate buffer (pH 6.8) at 259 nm with regression coefficient of 0.998 following to the equation Y=0.043x+0.003. The FT-IR spectra study also checks the drug - polymer interaction. Development was started with guar gum. At the same time to enhance the matrixing ability of the above HPMCK4 was also been used. Thiocolchicoside was found to be compatible with the guar gum and other excipients selected in the present studies like HPMC K4M and PVP etc.
After preformulation work, matrix tablets of drug were prepared by non aqueous wet granulation method. Initially the concentration of polymer was optimized and prepared formulation G-1 to G-3 were evaluated and observed that it was not self sufficient to achieve desired matrixing ability for desired time. So further, HPMC K4M was also incorporated into the formulations to form GH-1 to GH3. On the basis of obtained results and release of the drug formula GH-2 was selected. But the release of the drug in this formulation was not optimum so for increasing the release of the drug formulation GH-2, the concentration of lactose as channeling agent was further optimized to improve the release of the drug from polymer matrix. In this regard, Formulations GHL-1 and GHL-2 were prepared and evaluated for the various properties in comparison to GH-2. The drug release study of the formulation GHL-1 and GHL-2 both are showing good release but the formulation GHL-1 get deform during the study so formulation GHL-2 was taken for further study with release of 94.56%. To find out the mechanism of drug released from the final formulations GHL-1 and GHL-2 of thiocolchicoside matrix tablets, the data was fitted to zero order, first order and Higuchi model.

Keywords: Matrix Tablet, Thiocolchicoside, Guar Gum, Natural Polymer

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and supple design of dosage form[1]. Matrix tablets are the kind of tablet which is aimed such that it releases its substances regarding first order kinetics or zero order kinetics due to distinctive procedure and combination of hydrophobic and hydrophilic polymers as an excipient to form a matrix[2,3,4,5].
Thiocolchicoside is a muscle relaxant with anti-inflammatory and analgesic effects[6]. It acts as a competitive $GABA_A$ receptor antagonist and also glycine receptor antagonist with similar potency and nicotinic acetylcholine receptors to a much lesser extent. It has powerful convulsant activity and should not be used in seizure prone individuals. Thiocolchicoside is having a half life of 5-6 hrs. The bioavailability of Thiocolchicoside tablets is approximately 25% absorbed with first pass metabolism and the serum concentration touches its peak within 1-2 hrs after oral administration[7]. Guar gum is a biodegradable polysaccharide extracted from guar or cluster bean, called as Guar gum has been found to have a wide application in pharmaceutical industry[8].
In present, work we have explored the matrixing ability of HPMC and guar gum polymers for the prolonged delivery of Thiocolchicoside, which have very little half life and number of adverse effects are associated with it. So it may be a good applicant for such delivery.

Materials and methods

Thiocolchicoside was obtained as Gift sample from SarvBiolabSirmour, H P. Guar gum, HPMC K4M, Lactose, magnesium stearate, Talc and ethyl alcohol obtained from Himedia chemicals Mumbai. Other reagents used are analytical grade.

Preformulation Study

Organoleptic evaluation of thiocolchicoside drug: Organoleptic evaluation was evaluation in which we observed the physical properties of the drug like color, odor, test, physical state etc.
Solubility determination of thiocolchicoside: Solubility of Thiocolchicoside was tested in various solvents. A definite amount (10mg) of drug was dissolved in exact amount (10ml) of solvents at room temperature and observed by the uv- visible spectrometer.

Melting point of Thiocolchicoside: Melting point of Thiocolchicoside was determined by Theils Apparatus. It is performed by filling of drug in capillary tube and tied this capillary tube at the bottom of thermometer with the help of thread. Now filled Theils tube with light liquid paraffin and holded this tube with the help of burette stand than place burner at the bottom of tube, dip the thermometer in this liquid paraffin and then note the point which drug started melting in the capillary.

Partition Coefficient of Thiocolchicoside: The partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium. For a drug delivery system, Lipophilic/Hydrophilic balance has been shown to be a contributing factor for rate and extent of drug absorption. Partition coefficient provides a mean of characterizing Lipophilic/Hydrophilic nature of drug. The measurement of drug lipophilicity is an indication of its ability to cross the lipoidal cell membrane.

UV Spectrophotometric study of thiocolchicoside

Preparation of stock solution 10mg of exactly weighed Thiocolchicoside was dissolved in adequate quantity of 6.8pH bufferin 10ml volumetric flask and shaken (1000 µg/ml). The volume was made upto 10ml

UV-Scanning ofthiocolchicosidein 6.8pH buffer to Determination of λ_{max}
1ml solution was taken from the stock solution in 10ml volumetric flask and make upto 10ml with 6.8pH bufferresultant solution was100 µg/ml.
10µg/ml, Aliquot was scanned between 200-400 nm on a UV-Visible spectrophotometer against 6.8pH bufferas blank.

Preparation of standard curve 6.8pH buffer Aliquots of the above solution were taken and dilute to get drug concentration in the range of 5-25 µg/ml. The resulting dilutions (5-25 µg/ml) were scanned and Absorbance was measured by using UV/Visible spectrophotometer at λ_{max} 259 nm against 6.8pH bufferas blank. Linear regressed calibration curve was created.

Compatibility studies of Thiocolchicoside with excipients: Compatibility study of Thiocolchicoside with excipient was performed under different storage condition for one month. Drug and excipients were physically mixed and the physical mixture was divided in four parts, filled in glass vial and kept under different temperature and relative humidity condition. The control sample and a vial containing only drug was sealed and kept as such in low temperature condition (2-8^{0}C). After one month the samples were withdrawn and physically observed for change in the physical characteristic of the drug-excipient mixture.

IR Spectroscopic study for Drug Excipients Interaction: The IR spectra of drug and polymer (HPMC) in ratio (1:1) were recorded to determine the suitability of selected polymer for Thiocolchicoside using Infrared spectrophotometer. The IR analysis was performed with spectra measures over the frequency range 750-4000 cm^{-1}. The study was performed on FT-IR spectromrter, observed the spectra for, major deviation in comparison to the spectra of standard drug.

Method of formulation of Granules
Granules were prepared by wet granulation method. Guar gum and thiocolchicoside were mixed homogeneously by pestle mortar. Lactose was used as filler and channeling agent. PVP solution in Ethanol was used as granulating agent. Granules were prepared by 30 mesh screen. Prepared granules were dry on hot air oven and stored in dry and cool place or in desiccator.

Characterization of prepared granules
Bulk density (D_b): It is the ratio of the total mass of the granules to the bulk of volume of the granules. It was measured by poured the weighed granules (passed through standard sieve) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density was calculated according to the formula mention below. It is expressed in g/cc and is given by-

$$D_b = m/V_0$$

\Where,
m – mass of the granules
V_0 – bulk volume of the granules

Tapped density (D_t): It is the ratio of total mass of granules to the tapped volume of the granules. The volume was measured by tapping the granules for 50 times. Then the tapping was done. Then the tapping was done for 75 times and the taped volume was noted (the different between these two volume should be less than 2%). If it is more than 2% tapping is continue for 125 times and tapped volume was note.

$$D_t = m/V_I$$

Where,
m – Mass of the granules
V_I – tapped volume of the granules

Angle of repose (θ): This is the maximum angle possible between the surface of a pile of the granules or granules and the horizontal plane.

The angle of repose of granules was determined by the funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The granules sample was passed through the funnel until it forms a heap. Further, adding of the granules was stopped as soon the heap touches the tip of the funnel. The circle was drawn across it without disturbing pile. The radius and the height of the heap were noted down. The same procedure was repeated for three times and the average value was taken. The angle of repose was calculated by using equation.

$$\text{Tan } \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose

h = Height of the heap

r = Radius of the heap

Measurement of granules Compressibility

(a) Compressibility Index

The flow ability of the granules can be evaluated by comprising the Bulk Density (BD) and Tapped Density (TD) of granules and the rate at which it packed down. Compressibility Index of the granules was determined by the carr's compressibility index:

$$CI\ (\%) = TD\text{-}BD/TD \times 100$$

Hausner'sRatio : It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5, it was determined by the ratio of tapped density and bulk density.

$$HR = \text{Tapped Density/ Bulk Density}$$

Formulation of Matrix Tablets

In Granules, talc (5% w/w) and magnesium stearate (5% w/w) were added as a glidant and lubricant respectively. Tablets were compressed using 9 mm die/punch set in a single punch tablet compression machine.

Evaluation of Prepared Matrix Tablets

The evaluation of Matrix tablet dosage form with respect to various characteristics is vital to precisely control the dosage form behavior and to ensure batch-to-batch uniformity. The tablets were evaluated for thickness, weight variation, hardness, friability, matrixing property and *in vitro* drug release.

Thickness: The thickness of the tablets was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated.

Weight variation Test: To study weight variation, 20 tablets were weighted individually and the arithmetic mean weight calculated. Not more than two tablets differ from the average weight by more than 5%.

Swelling behavior of the Tablet: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied in a petridish containing pH 6.8 phosphate buffers. At the end of 0.5h and 1 h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 1 h, weights of the tablet were noted, and the method was continued till the end of 8 h. Percentage weight gain by the tablet was calculated by formula;

$$S.I = \{(Mt\text{-}Mo) / Mo\} \times 100$$

Where,

S.I = swelling index,

Mt = weight of tablet at time t (h) and

Mo = weight of tablet at zero time

***In-vitro* Drug release study:** *in-vitro* release studies were carried out in the dissolution test apparatus USP Type II. The tests were done out in 900 ml of 6.8 pH Phosphate buffer for 12 hrs at 75 rpm at 37±0.5ºC. 5 ml of the aliquot were withdrawn at different predetermined time intervals (1, 2, 4, 6, 8, and 12) and filtered. Sample was analyzed at 259 nm using UV/Visible spectrophotometer, 6.8pH Phosphate buffer was used as blank. 5 ml of 6.8 pH Phosphate buffer was replaced in the vessel after each withdrawal to maintain the sink condition. The percentage drug release was calculated using the calibration curve and was plotted against function of time to study the pattern of drug release from tablets.

Optimization of Formulation The duty of formulating a dosage form to accomplish a desirable controlled release with the selection of potential excipients that allow the formulation of matrices having controlled delivery characteristics, and it should dissolve slowly enough to work as a reservoir for the delivery. Initial dummy batches were prepared using guar gum.

Optimization of 'Drug: Polymer' Ratio In preliminary trial batches, dummy batches were prepare by using guar gum in same ration as expected to take in final batches with okra gum. Ratio of drug and guar gum were optimized to get better matrixing property and prolonged release for the desired time. Three formulations comprising changed ratio of guar gum is mentioned in the table.

Statistical Treatment of Data

In order to determine the mechanism of drug release from sustained release floating matrix tablets, the data were treated using following mathematical models-
1.Zero order (cumulative percentage of drug released versus time)
2. First order (log percent of drug unreleased versus time)
3. Higuchi square root law (cumulative percentage of drug released versus square root of time)
4. Korsmeyer's model (log of cumulative percentage of drug released versus log time)

Result and Discussion

The organoleptic properties of thiocolchicoside were solid, yellow odorless powder. The melting point was observed at 194-1970C. The spectral study was start with drug analysis and preparation of calibration on a UV-Visible spectrophotometer. The linearity was achieved in the concentration range of 5-25 µg/ml in phosphate buffer (pH 6.8) at 259 nm with regression coefficient of 0.998 following to the equation Y=0.043x+0.003. The FT-IR spectra and DSC study also checks the drug.
Development was started with guar gum. At the same time to enhance the matrixing ability of the above HPMCK4 was also been used. To rule out any type of physical incompatibility between drug and excipient, 1:1 blends of drug and excipient were kept under different temperature conditions. Thiocolchicoside was found to be compatible with the guar gum and other excipients selected in the present studies like HPMC K4M and PVP etc.
The interference of selected polymer was also studied to rule out the negative effects because of polymer. Spectrophotometric estimation of Thiocolchicoside in presence of guar gum was studied and it was found that that there is no major change in absorbance or wavelength. The IR spectra of drug and polymer combination show no major deviation, in comparison to the spectra of standard drug. At the same time DSC thermogram of drug-polymer combination shows no major deviation from the standard with the peak at about 213^{o}C
After preformulation work, matrix tablets of drug were prepared by non aqueous wet granulation method. Initially the concentration of polymer was optimized to get better matrixing property and sustain release of the drug, prepared formulation G-1 to G-3 were evaluated and observed that it was not self sufficient to achieve desired matrixing ability for desired time.
So further, HPMC K4M was also incorporated into the formulations to form GH-1 to GH3. On the basis of obtained results and release of the drug formula GH-2 was selected with release of total 84.41% drug release. But the release of the drug in this formulation was not optimum so for increasing the release of the drug formulation GH-2, the concentration of lactose as channeling agent was further optimized to improve the release of the drug from polymer matrix. In this regard, Formulations GHL-1 and GHL-2 were prepared and evaluated for the various properties in comparison to GH-2 and the results are mentioned in the table no. 18, 19 & 20. The drug release study of the formulation GHL-1 and GHL-2 both are showing good release but the formulation GHL-1 get deform during the study so formulation GHL-2 was taken for further study with release of 94.56%. During the study it was also been saw that if the concentration of lactose is increased more than optimum it resulted in the burst release of the formulation which in not desired so the formulation with higher lactose was not considered for the drug release study.
To find out the mechanism of drug released from the final formulations GHL-1 and GHL-2 of thiocolchicoside matrix tablets, the data was fitted to zero order, first order and Higuchi model.
When the data obtained for release of drug for final formulation GHL-1 and GHL-2 were plotted according to the first order equation, the formulation shows a fair linearity, with correlation coefficient values of 0.967 and0.965 respectively which indicates greater the concentration faster the release rate of drug from tablet.
Release of the drug from a matrix tablet containing hydrophilic polymers generally includes factor of diffusion. Diffusion is related to transport of drug from the dosage matrix in to the *in vitro* study fluid depending on the concentration. As gradient varies, the drug was released and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which was referred as square root kinetics or Higuchi's kinetics. In this experiment, the *in vitro* release profiles of drug the formulation could be best expressed by Higuchi's equation showing high linearity for both the formulation GHL-1 and GHL-2, representing the release process under the drug diffusion through polymer matrix..

Conclusion

Quantitative estimation of Thiocolchicoside in formulation was carried out by UV/Visible spectrophotometer. The work was started with the preparation of calibration curve in 6.8 pH Phosphate buffer. The methods have shown to follow the Lambert beer law in range of 5-25 µg/ml with the regression coefficient of 0.998.
Conclusion Quantitative estimation of Thiocolchicoside in formulation was carried out by UV/Visible spectrophotometer. The work was started

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Table no. 8: *In vitro* drug release of batch GH2 and GH3

Time(hr)	Cumulative Percentage Drug Release	
	GH2±SD	GH3±SD
0	0	0
1	18.42±1.21	15.21±0.42
2	28.93±1.5	26.29±0.34
4	42.24±.89	38.48±1.2
6	53.82±1.4	48.44±1.3
8	72.38±2.04	62.25±2.04
12	78.84±0.82	73.87±1.8
24	82.41±1.82	78.45±1.23

Table no. 10: Hardness, thickness and diameter Thiocolchicoside tablets

S. No.	Parameter	Formulation code		
		GH2	GHL-1	GHL-2
1.	Hardness (kg/cm^2)	5.4 ± 0.43	5.5 ± 0.5	5.5 ± 0.41
2.	Thickness (mm)	2.1	2.3	2.5
3.	Diameter (mm)	9.1	9.1	9.1

Drug-polymer interaction study was performed with FT-IR and DSC study, the data and spectra related to the study shows no interaction of polymers with the Thiocolchicoside.

The use of hydrophilic polymer matrix is one of the most widespread approaches in formulating an extended-release dosage form. This is due to the fact that these formulations are relatively flexible and a well-designed system usually gives reproducible release profile. In the present work initially the polymers: drug ratio was optimized to get the better matrixing property and sustained release of the drug. The optimum ratio of drug-polymer was found to be 1:2 in formulation GHL-2.

In the present study it was found that Hydroxypropyl methylcellulose (HPMC) in combination with guar gum can be successfully used for the formulation of matrix tablet of Thiocolchicoside without any interference with Thiocolchicoside, it can also be concluded that this polymer alone or in combination with other polymers may be used for the formulation of any drug delivery system where matrix formation is required.

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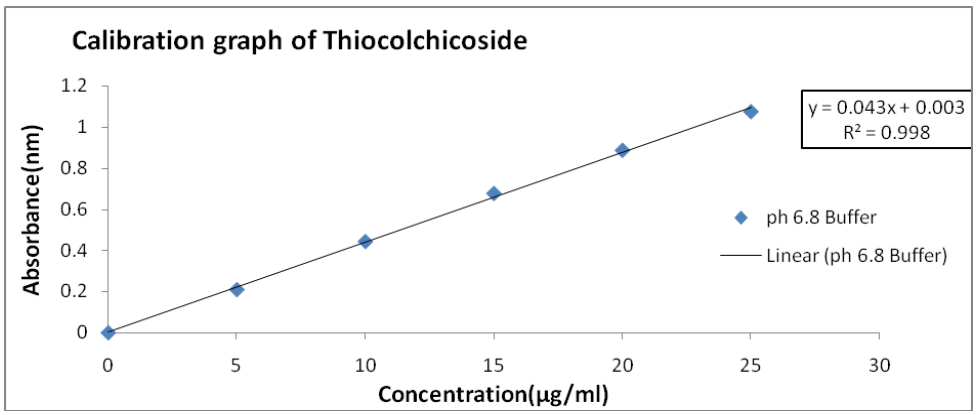

Figure no.1: Graph showing calibration curve of Thiocolchicoside (pH 6.8 buffer)

Table no. 1: Physical drug-polymer compatibility studies

S. No.	Drug-Excipient	Initial	7 Days study			Comments
			Condition			
			CS	RT	Oven	
1.	Drug +Polymer (1:1)	Cream Color	NC	NC	NC	Compatible
2.	Drug +Polymer (1:1)	Cream Color	NC	NC	NC	Compatible
3.	Drug +Polymer (1:1)	Cream Color	NC	NC	NC	Compatible
4.	Drug +Polymer (1:1)	Cream Color	NC	NC	NC	Compatible
5.	Drug +Polymer (1:1)	Cream Color	NC	NC	NC	Compatible

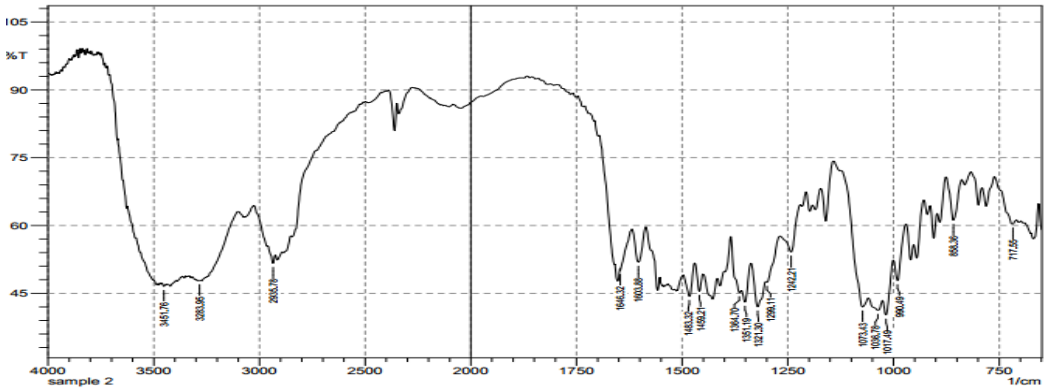

Figure no. 2: IR graph of drug (Thiocolchicoside) and polymer (HPMC)

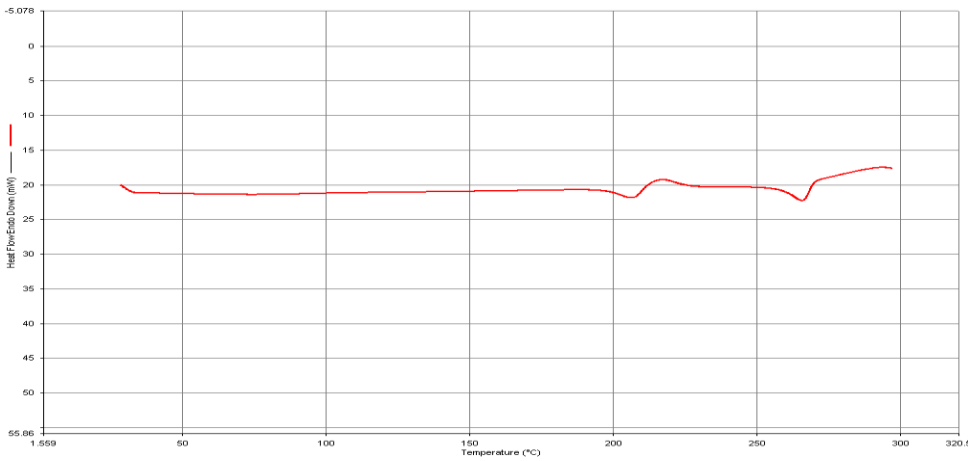

Figure no. 3: DSC graph of (Thiocolchicoside) and polymer (guar gum and HPMC)

Table no. 2: Micromeritic properties of granules

Formulation	Parameter				
	BD (g/ml)	TD (g/ml)	CI (%)	HR	Angle of Repose
G-1	0.65±0.02	0.77±0.02	15.78±0.13	1.18±0.01	30.96±0.23
G-2	0.53±0.02	0.63±0.01	15.12±0.041	1.19±0.01	28.56±0.21
G-3	0.53±0.01	0.66±0.01	13.63±0.11	1.15±0.02	28.2±0.13
GH1	0.54±0.01	0.66±0.01	16.66±0.16	1.2±0.01	28.24±0.19
GH2	0.64±0.01	0.71±0.01	11.26±0.07	1.12±0.02	29.1±0.21
GH3	0.60±0.01	0.74±0.01	18.91±0.13	1.23±0.01	28.8±0.23

Table no. 3: Formulation of Thiocolchicoside matrix tablet with different concentration of Guar gum

S. No.	Ingredients (mg/tab)	G-1	G-2	G-3
1.	Drug (Thiocolchicoside)	16	16	16
2.	Guar gum	80	100	120
3.	Lactose	54	54	54
4.	PVP K_{90} in alcohol 1% w/v	10	10	10
5.	Talc	5	5	5
6.	Mg stearate	5	5	5
7.	Total weight of tablet	170	190	210

Table no. 4: Formulation of Thiocolchicoside matrix tablet containing Guar gum with different concentration of HPMC

S. No.	Ingredients (mg/tab)	GH-1	GH-2	GH-3
1.	Drug (Thiocolchicoside)	16	16	16
2.	Guar gum	80	80	80
3.	HPMC K4M	40	50	60
3.	Lactose	44	44	44
4.	PVP K_{30} in alcohol 1% w/v	10	10	10
5.	Talc	5	5	5
6.	Mg stearate	5	5	5
7.	Total weight of tablet	200	210	220

Table no. 5: Hardness, thickness and diameter Thiocolchicoside tablets

S. No.	Parameter	Formulation code		
		GH1	GH2	GH3
1.	Hardness (kg/cm^2)	4.5 ± 0.5	5.4 ± 0.43	5.6 ± 0.31
2.	Thickness (mm)	2.4	2.6	2.8
3.	Diameter (mm)	9.1	9.1	9.1

Table no. 6: General characteristics of tablets

Code	Weight variation test (%)	Content Variation	Hardness (Kg/cm^2)	% Friability	Swelling Index
GH1	3.52± 0.11	95.6%	4.5 ± 0.5	0.24	54
GH2	4.25 ± 0.17	94.8%	5.4 ± 0.43	0.21	61
GH3	5.32 ± 0.08	92.4%	5.6 ± 0.31	0.17	68

Table no. 7: Swelling Index and observation for swelling

Sr. No	Formulation	Swelling Index	General observation related to swelling
1.	G-1	42	Swell and burst (not able to measure)
2.	G-2	46	Slow swell But get deform after 2-3 hr

3.	G-3	51	Swelling occurs but get deformed
4.	GH1	54	Slow swelling but get deformed
5.	GH2	61	Slow swelling
6.	GH3	68	Slow swelling

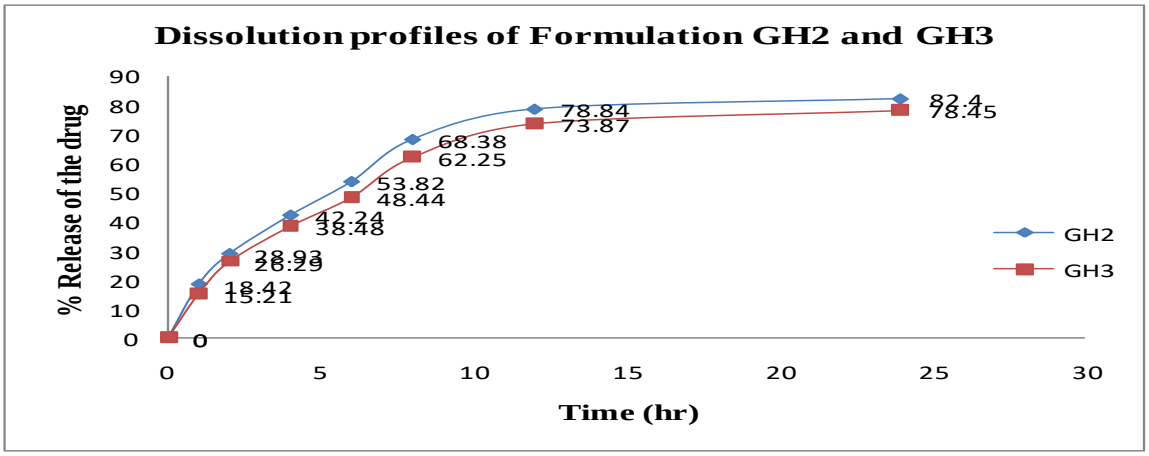

Figure no. 4: Dissolution profiles of Formulation GH2 and GH3

Table no. 9: Formulas for Thiocolchicoside matrix tablet containing different concentrations of lactose

S. No.	Ingredients (mg/tab)	GH-2	GHL-1	GHL-2
1.	Drug (Thiocolchicoside)	16	16	16
2.	Guar gum	80	80	80
3.	HPMC K4M	50	50	50
3.	Lactose	44	54	64
4.	PVP K_{30} in alcohol 1% w/v	10	10	10
5.	Talc	5	5	5
6.	Mg stearate	5	5	5
7.	Total weight of tablet	200	220	230

Table no. 11: General characteristics of tablets

Code	Weight variation test (%)	Content Variation	Hardness (Kg/cm^2)	% Friability	Swelling Index
GH2	5.15 ± 0.27	96.4%	5.4 ± 0.43	0.11	61
GHL-1	5.82 ± 0.61	96.2%	5.5 ± 0.5	0.13	63
GHL-2	6.52 ± 0.54	94.3 %	5.5 ± 0.41	0.09	71

Statistical Treatment of Data

6.8.1 Zero order kinetics of GHL-1 and GHL-2

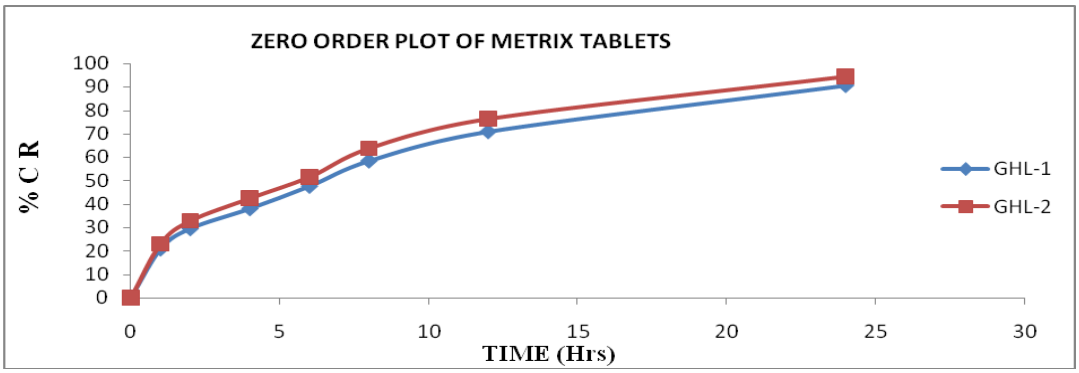

Figure no. 5: Zero order plot for matrix tablets

6.8.2 First order kinetics for GHL-1 and GHL-2

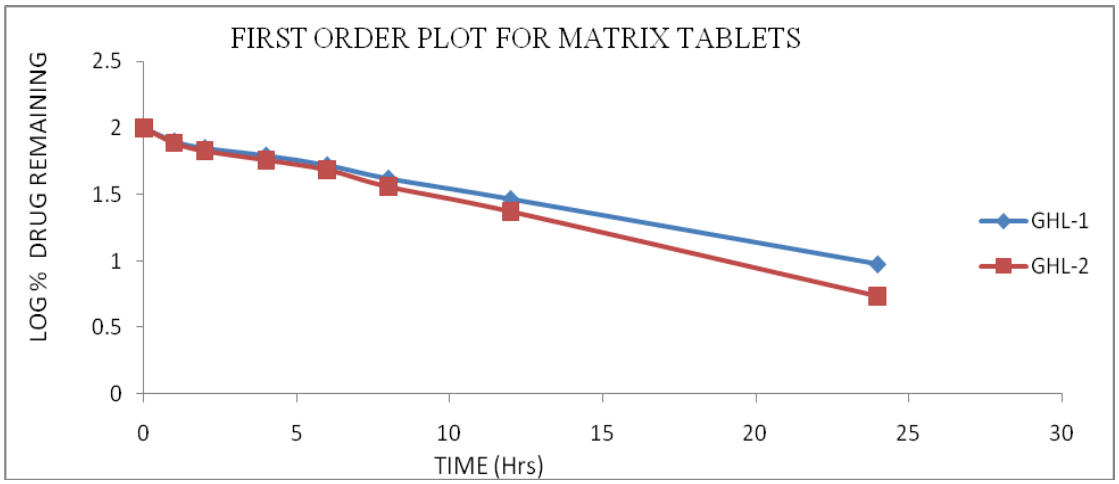

Figure no. 6: First order plot for matrix tablets

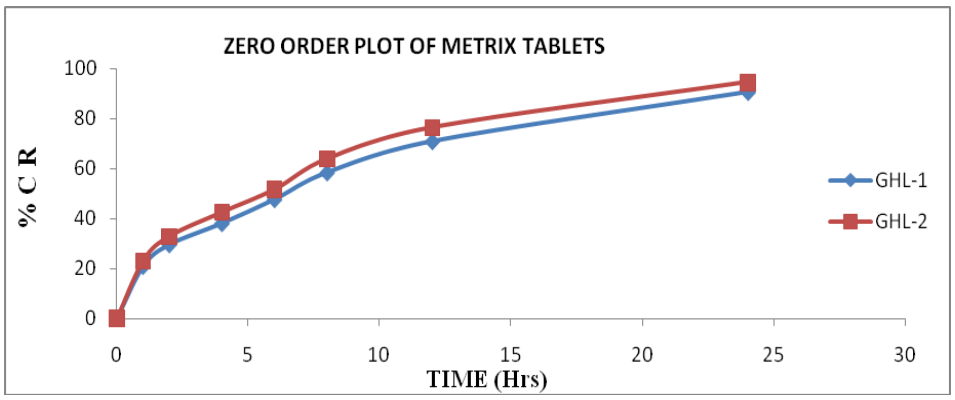

Figure no. 7: Zero order plot for matrix tablets

6.8.2 First order kinetics for GHL-1 and GHL-2

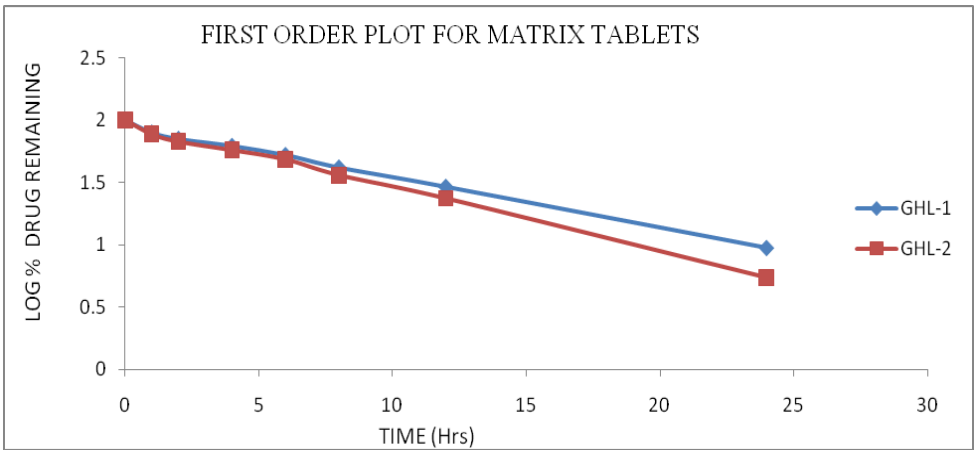

Figure no. 8: First order plot for matrix tablets