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FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE TABLETS OF METHYLCOBALAMIN BY USING POLYMER MATRIX SYSTEM

Nishant Kumar Sharma
Sanskar College of Pharmacy & Research, Ghaziabad, 201302, Uttar Pradesh, India

Ajeet
Sanskar College of Pharmacy & Research, Ghaziabad, 201302, Uttar Pradesh, India

Babita Kumar
Sanskar College of Pharmacy & Research, Ghaziabad, 201302, Uttar Pradesh, India

Corresponding author:
Nishant Sharma
Email:
nishantsharma2153@gmail.com

ABSTRACT

Methylcobalamin is a medication commonly prescribed for anemia conditions linked to thick or excessive mucus production.

The sustained-release tablets of Methylcobalamin are prepared using the wet granulation technique. A total of 6 batches were prepared. Dissolution profile and absorption or release of drug within 12 hours. Identification of drug purity was done through FTIR. The FTIR analysis showed that the spectra of the pure drug and the formulation ingredients were largely similar. The FTIR profile of the drug matched the reference spectrum for pure Methylcobalamin, confirming its purity.

The Tapped density of various formulation were varies between 0.55-0.70 (gm/ml). According to the post compression parameter of all formulations are given as well as following. In the prepared formulations, tablet hardness was consistently above 2.0 kg/cm², reflecting adequate mechanical strength. Additionally, the friability values for formulations 1 through 6 were all below 1%, demonstrating that the tablets possessed excellent resistance to abrasion and maintained their integrity.

Among the sustained release Methylcobalamin tablets, formulation F-5 demonstrated the best performance, as it released at least 90% of the drug within 12 hours.

Keywords: Sustained release, Tablets, Polymers, Matrix system, Methylcobalamin

INTRODUCTION

Oral drug delivery system

Oral administration remains the preferred method for delivering medications because it is easy to use, encourages patient adherence, and allows for versatile formulation options. The majority of commercially available drug delivery systems utilize the oral route. Over time, these systems have evolved from providing immediate drug release to enabling targeted delivery at specific sites within the body.[1]

Patients generally favor drug delivery methods that require only a single dose or infrequent dosing throughout their treatment period. Therefore, pharmacists aim to design single-dose therapies that come as close as possible to this ideal. Much research has focused on developing controlled or sustained release systems to maintain therapeutic drug levels over extended periods, addressing challenges like poor solubility, limited bioavailability, dosing frequency, stability, and potential toxicity. These efforts have led to the creation of innovative drug delivery technologies.[2,3]

Unlike conventional tablets or capsules, which release drugs without regulating delivery, controlled release systems offer more precise management of drug absorption. Various oral delivery approaches have been developed, including rate-controlled, time-controlled, and site-specific systems.[4,5]

For drugs that are not fully absorbed, the time spent in the intestine becomes a key factor in their overall absorption.

GASTROINTESTINAL TRACT (GIT)

The human gastrointestinal tract (GI tract or GIT) is a system of organs that manages the intake and breakdown of food, absorption of nutrients, and removal of waste products. In contrast, the term "digestive system" refers to a wider network that includes additional organs involved in digestion. The GI tract also produces hormones such as gastrin, secretin, cholecystokinin, and ghrelin, which play key roles in controlling digestive activities. Structurally, the tract is divided into upper and lower parts, with the intestines further separated into the small and large intestines.[6,7]

Conventional dosage form:

Traditional dosage forms often result in significant variations in drug levels within the blood and tissues, which can cause unwanted side effects and reduced therapeutic effectiveness. Issues like the need for frequent dosing and inconsistent absorption have driven the development of controlled drug delivery systems.[8]

Limitations

- Low adherence to medication schedules increases the likelihood of missed doses.
- Irregular drug levels can cause unpredictable peaks and troughs in the bloodstream.
- Using several medications at once raises the risk of adverse effects and can make treatment more expensive.

Types of extended-release devices

a) *Controlled release (CR):*

b) *Prolong Action:*

Long-acting or extended-action products are formulations that include a prodrug of the active ingredient, which is characterized by an extended biological half-life.[9,10]

c) Sustained Release:

In case of sustained release (SR) dosage forms the release of the drug is slower than conventional dosage form.

Advantages of Sustained Release Drug Delivery:[11,12]

- Enhanced therapeutic outcomes
- Reduction in unwanted side effects
- Greater convenience and better adherence for patients
- Cost-effectiveness
- Sustained release formulations are generally more affordable compared to traditional dosage forms
- Lower nursing costs due to less frequent drug administration
- Minimized fluctuations in blood levels that are typical with repeated dosing of standard medications

Disadvantages:

- Risk of rapid release of the entire drug dose (dose dumping)
- Limited ability to quickly adjust doses in urgent situations
- Challenges in establishing a reliable relationship between lab results and actual performance in the body
- Variability in patient response
- Sustained release formulations can be more costly
- These medications are not recommended for individuals with compromised gastrointestinal absorption or kidney issues
- Drugs with naturally long biological half-lives, such as digitoxin, are not ideal candidates for sustained release preparations[13,14]

The aim of the study was to formulate and evaluate sustained release tablets of methylcobalamin by using polymer matrix system.

MATERIALS AND METHODS

MATERIALS

The materials used in this study were of laboratory grade and were provided by the institution.

METHODOLOGY

Drug identification/Pre formulation studies

Melting point

A small amount of the drug will be placed into a capillary tube that is sealed at one end. This tube will then be inserted into a digital melting point apparatus.[15,16]

Solubility

To assess the solubility of Methylcobalamin, the compound was tested in water, ethanol, methanol, and chloroform. An excess amount of the drug was incrementally added to 10 ml of each solvent in separate beakers, which were then sealed with aluminum foil. These mixtures were shaken and left undisturbed

for 24 hours to reach equilibrium.[17]

UV spectrophotometric determination

To prepare the standard stock solution, 50 mg of Methylcobalamin was dissolved in 50 ml of methanol and then sonicated in a bath sonicator for 15 minutes to ensure complete dissolution. This resulted in a stock solution with a concentration of 1 mg/ml (1000 µg/ml or 1000 ppm). From this stock, further dilutions were made to obtain solutions ranging from 2 to 10 ppm. These diluted samples were analyzed using a UV-Visible spectrophotometer to scan for their maximum absorbance (λmax) and to determine the characteristic wavelength for Methylcobalamin HCl.[17,18,19]

FTIR

KBr pellets will be formed by applying manually broken down and re-sieved through the same mesh to achieve uniform granule size. Then sifted lubricants as HPMC K-15 M, HPMC Methocel K4M, Colloidal Silicon Dioxide (Aerosil 200) & Talc through #40 & collected in separate polybag. Then sifted Magnesium Stearate through #60 & collated separately.[20,21]

hydrostatic pressure of 6–8 tons using a KBr press. The FTIR spectra will then be collected over a scanning range of 400 to 4000 cm^{-1}.

Fabrication of tablets

Granules intended for the sustained release tablets containing 1500 mcg (1.5 mg) of Methylcobalamin were produced using the wet granulation method. Firstly sifted HPMC K4M, HPMC K15M, Microcrystalline Cellulose & Di Calcium Phosphate (Anhydrous) through #40 & collected in polybag. Then sifted Methylcobalamin through #100 triturate with the fines of above sifted materials. Geometrically mixed sifted Methylcobalamin with sifted materials to make bulk. Dry mixing is then done for 10 minutes in double polybag. [22,23,24]

Lubrication is then done by mixing dried sifted granules & lubricants in blender for 15 minutes then added sifted magnesium stearate & further blending is done for 03 minutes & final in-process parameters checked.

Table 1: Composition of Methylcobalamin Matrix Tablets

Ingredients (mg/tablet)	1	F2	F3	F4	F5	F6
Methylcobalamin	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**
HPMC K-15 M	20	20	30	40	68	70
C Methocel K4M	40	50	45	25	38	40
crocrystalline Cellulose	90	70	66	82	60	65
Di Calcium Phosphate	81	91	87	73	61.5	55

(Anhydrous)						
Polyvinyl Pyrrolidone (K-90)	3	3	4.5	4.5	6.0	5.0
sopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	1.5	1.5	2.0	2.0	2.0	2.0
HPMC K-15 M	20	30	20	25	22	22.5
C Methocel K4M	40	30	40	45	37	35
Colloidal Silicon Dioxide (Aerosil 200)	1.5	1.5	2.0	2.0	2.0	2.0
agnesium Stearate	1.5	1.5	2.0	2.0	2.0	2.0
Weight of Uncoated Tablets = 300 mg Each Tablet						
Coating Procedure: 2% Coating						
orcoat FC4S- 1 (Brown)	6.0	6.0	6.0	6.0	6.0	6.0
Dichloromethane (Methylene Dichloride)	78.0	78.0	78.0	78.0	78.0	78.0
Isopropyl alcohol	48.0	48.0	48.0	48.0	48.0	48.0
Weight of coated table = 306 mg						

Evaluation parameters

Weight Variation Test:

To confirm that each tablet contains the correct dosage, the tablet weights will be assessed.[25]

Hardness:

The hardness of the tablets will be measured using a Monsanto hardness tester.[26]

Friability:

Initially, the tablets are weighed and then subjected to 100 rotations (lasting 4 minutes) in the apparatus.[27]

Thickness and diameter:

These parameters will be determined using Vernier calipers.[28]

Loss on Drying:

Measure 1.0 g of the sample and dry it using a Loss on Drying (LOD) apparatus set at 60°C.

Determination of Percentage Yield

The yield percentage for the prepared formulations was determined by comparing the final weight of the product to the initial total amount of drug and polymers used in the process.[30]

Angle of Repose:

A funnel was filled completely, and the sample was allowed to flow freely through the opening by gravity. The resulting powder cone formed on a graph paper was used to assess the area of the pile, which helps evaluate the powder's flow properties.[31]

In-Vitro Disintegration Test:

The disintegration test was conducted on six tablets using phosphate buffer at pH 6.8, maintained at 37°C ± 2°C as the medium. The time required for each tablet to fully disintegrate, leaving no visible residue, was recorded in seconds or minutes.[32,33]

In-Vitro Drug Release Profile:

In-vitro dissolution testing was carried out using a USP type I dissolution apparatus set at 50 rpm. The study spanned 8 hours, beginning with 900 ml of 0.1 N HCl (pH 1.2) as the dissolution medium at 37 ± 0.5°C for the initial 2 hours, followed by 900 ml of pH 7.4 phosphate buffer for the remaining duration.[34,35]

Release Kinetics:

The most suitable model was selected based on the best fit. *Stability Study:*

Since monitoring product degradation at room temperature can be a lengthy process, accelerated stability studies are employed to expedite the evaluation.

RESULTS

Organoleptic Characteristics:-

Table 2: The Organoleptic Properties of Methylcobalamin

S.NO.	Organoleptic Properties	Result
1.	Color	White
2.	Odor	Odourless
3.	Taste	Tasteless

Table 3: Determination of Melting Point:

Method Employed	Reported Melting Point	Observed Melting Point
	Methylcobalamin	Methylcobalamin
Capillary Fusion Method	>300°C	300 - 302°C

RESULT OF ANALYSIS

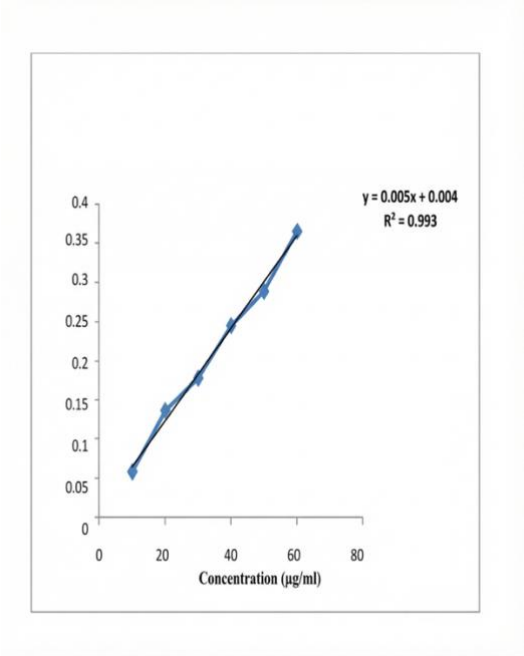

Fig. 1: Methylcobalamin calibration curve in phosphate buffer 6.8 pH at λmax-522 nm

Solution properties:

a) Solubility:

The relative solubility of different substances is represented using descriptive terms, as shown in the following table.

Table 4: Solubility study of Methylcobalamin

Sr. No.	Solvents and buffer	Results
1.	Acetonitrile	Partially soluble
2.	Ethanol	10 mg/ml
5.	Dimethyl sulfoxide	75 mg/ml
6.	Water	50 mg/ml

FTIR Compatibility study:

The FT-IR graphs are shown in figures that are given below:

Standard FTIR Spectra of Methylcobalamine:

Sample FTIR Spectra Methylcobalamine:-

The FTIR spectrum of Methylcobalamine which is performed by FTIR instruments is given as following and the interpretation of Methylcobalamine was found to be-

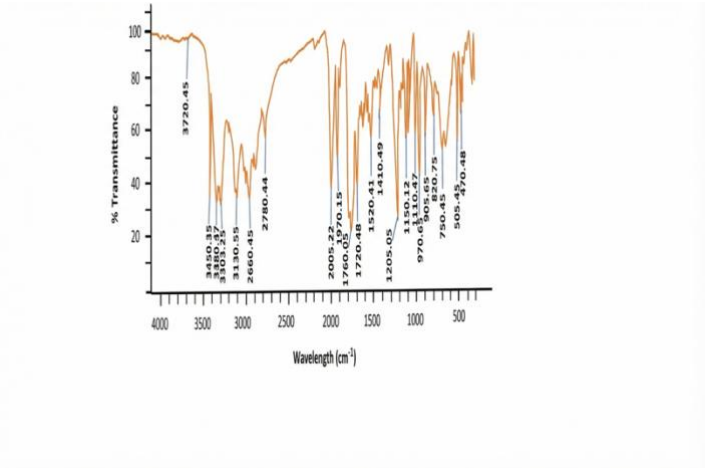

Fig. 2: FTIR Spectrum of Methylcobalamine (Sample)

Partition Coefficient (Log P) with Water & Chloroform:-

Partition coefficient is determined by the following solvents with both Aqueous & Non-Aqueous phase.

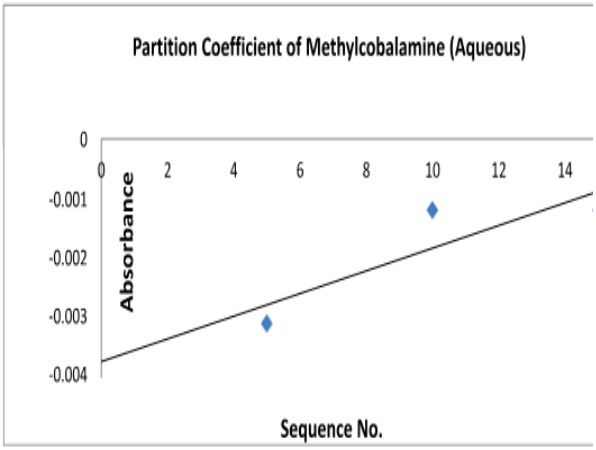

Fig. 3: Partition coefficient of methylcobalamin (aqueous)

OPTIMIZATION PRE-COMPRESSION PARAMETERS OF POWDER MIXTURE: -

Bulk Density: - (gm/ml.)

The bulk density followed expressed by a table of all formulations, it is given as well as following;

Table 5: Bulk Density of Methylcobalamin Sustained Release Tablet

S.NO.	F-1	F-2	F-3	F-4	F-5	F-6
1.	0.55	0.52	0.58	0.62	0.55	0.53
2.	0.59	0.56	0.54	0.58	0.58	0.52
3.	0.58	0.54	0.55	0.60	0.57	0.56
4.	0.60	0.56	0.56	0.59	0.58	0.51
5.	0.56	0.52	0.57	0.60	0.59	0.54
6.	0.60	0.54	0.56	0.61	0.61	0.58

OPTIMIZATION POST COMPRESSION PARAMETERS OF METHYLCOBALAMINE SUSTAINED RELEASE TABLETS:

Weight Variation : - (mg.)

It is given as well as following;

Table 6: Weight variation of Methylcobalamine Sustained Release Tablet

S.NO.	F-1	F-2	F-3	F-4	F-5	F-6
1.	302	304	300	302	305	308
2.	308	306	304	300	308	300
3.	304	301	303	304	308	301
4.	303	300	307	306	306	309
5.	302	308	309	304	304	303
6.	308	306	301	305	302	304
7.	303	308	306	300	304	301
8.	334	306	308	310	300	399
9.	399	301	304	305	307	300
10.	300	304	303	304	306	307
Mean ± S.D.	**303 ± 2.94**	**304 ± 2.91**	**304 ± 2.95**	**204 ± 2.94**	**305 ± 2.58**	**303 ± 3.64**

Hardness: - (kg/cm^2)

The Hardness of tablets followed expressed by a table of all formulations; it is given as well as following

Table 7: Hardness of Methylcobalamine Sustained Release Tablet

S.NO.	F-1	F-2	F-3	F-4	F-5	F-6
1.	1.8	2.1	2.7	2.6	3.0	3.4
2.	1.7	2.4	2.9	2.9	3.1	3.7
3.	1.4	2.2	3.0	2.6	3.3	3.8
4.	1.5	2.1	2.8	2.8	3.1	3.5
5.	1.8	2.8	2.6	2.9	3.4	3.4
6.	1.6	2.5	2.7	2.7	3.2	3.3
7.	1.4	2.6	2.8	2.8	3.3	3.6
8.	1.6	2.5	2.7	2.8	3.2	3.5
9.	1.5	2.4	2.8	3.0	3.3	3.7
10.	1.4	2.7	2.5	3.1	3.4	3.8
Mean ± S.D.	**1.57 ± 0.15**	**2.43 ± 0.24**	**2.75 ± 0.14**	**2.82 ± 0.16**	**3.23 ± 0.13**	**3.57 ± 0.17**

% Drug- Content : -

% Drug- content of Methylcobalamine Sustained Release Tablet.

Table 8: % Drug Content of Methylcobalamine Sustained Release Tablet

Formulations	Assay-1 (mcg)	Assay-2 (mcg)	Assay-3 (mcg)	Mean ± S.D. (mcg)	% Drug-Content
F-1	1501	1497	1504	1504 ± 0.010	100.26 %
F-2	1501	1505	1484	1496 ± 0.020	99.73 %
F-3	1511	1480	1512	1501 ± 0.015	100.06 %
F-4	1504	1495	1508	1497 ± 0.026	99.80 %
F-5	1490	1509	1506	1502 ± 0.020	100.13 %
F-6	1495	1488	1504	1495± 0.025	99.66 %

IN-VITRO DRUG RELEASE STUDY: -

Among the various sustained release tablets, the F5 formulation demonstrated the most favorable performance, achieving a complete drug release of 100.06% within 12 hours.

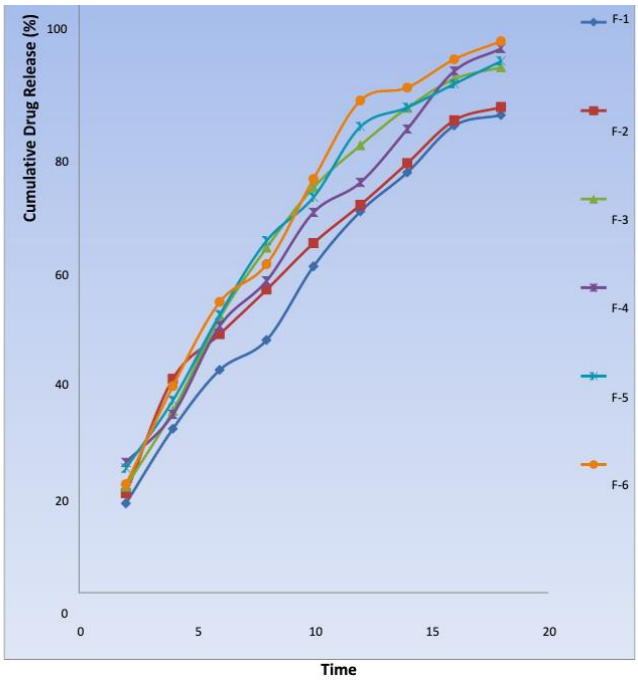

Fig.4: Cumulative % Drug release Methylcobalamine Sustained Release Tablet, of all formulations.

Release Kinetic Analysis: -

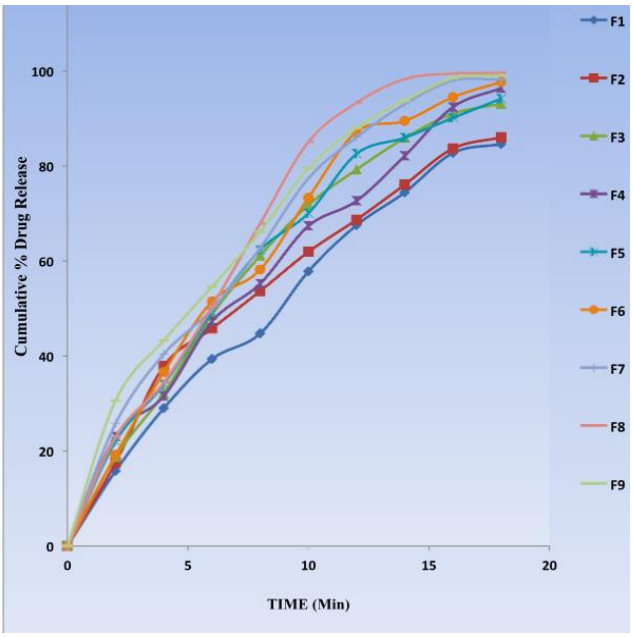

Fig. 5: Zero order release kinetic plot

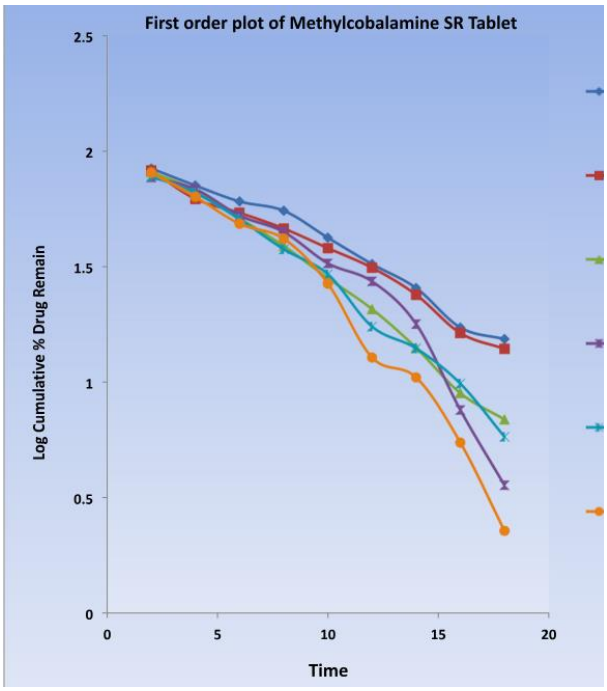

Fig. 6: First order release kinetic plot of Methylcobalamine Sustained Release Tablet.

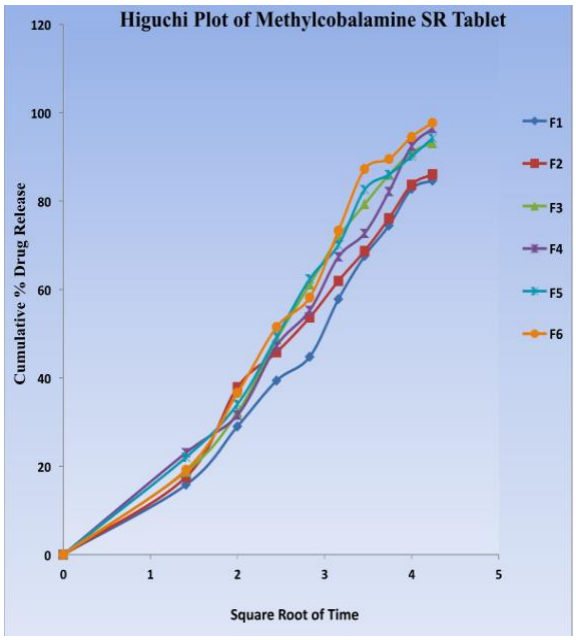

Fig. 7: Higuchi release kinetic plot of Methylcobalamine Sustained Release Tablet.

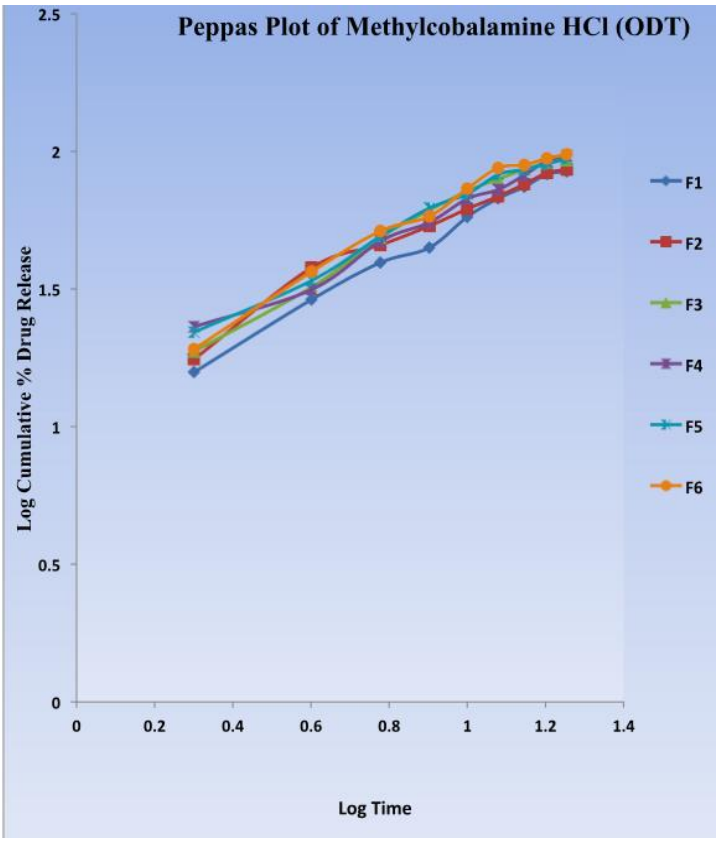

Fig. 8: Korsmeyer Peppas release kinetic plot of Methylcobalamine Sustained Release Tablet.

Dissolution Study Graphs of Formulation (F-5) by HPLC:

Dissolution study of Methylcobalamine Sustained release tablets was performed in time 1 hours, 8 hours and 12 hours.

IN-VITRO STABILITY STUDY:-

Table 9: In-Vitro % Release Result of stability study of optimized formulation, (F-)

S.No.	1 Hour	8 Hour	12 Hour
Initial Formulation % Release	22.97	46.46	96.45
After 3-Month % Release	24.97	47.46	97.45

DISCUSSION

Methylcobalamin is commonly utilized in the management of anemia, particularly in conditions associated with thick or excessive mucus.

Ingredients were combined in a geometric sequence and compressed using a tablet punching machine. This process produced SR tablets capable of releasing Methylcobalamin over a 12-hour period. The spectra of the pure drug and the final formulation showing no significant differences. Various concentrations of polymers were incorporated to facilitate tablet disintegration. Post-compression assessments revealed that tablet hardness was consistently above 2.0 kg/cm², indicating robust mechanical strength. Friability for all formulations remained below 1%, signifying excellent resistance to abrasion. Drug content was both high and uniform, exceeding 99.75% in all samples.

All formulations underwent accelerated stability testing to observe the effects of elevated temperature and humidity. Over the three-month period, no significant changes were noted in color, physical attributes, or drug content, indicating strong stability under stress conditions.

Of all the SR Methylcobalamin tablets tested, formulation F-5 demonstrated the most favorable performance, achieving a drug release of at least 90% within 12 hours.

CONCLUSION

All formulations underwent a physical stability assessment under various stress conditions to evaluate the impact of temperature and humidity, as outlined in regulatory guidelines. Various parameters were monitored and results indicated that most sustained release tablets containing Methylcobalamin HCl retained their color, size, and shape. Additionally, there were no significant changes observed throughout the three-month evaluation period. The stability tests showed that the tablets stayed stable when kept at 40°C (±2°C) and 75% (±5%) relative humidity.

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