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

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ABSTRACT

Methylcobalamin is the biologically active coenzyme form of vitamin B12 and is prescribed for vitamin B12 deficiency states, including megaloblastic anaemia and peripheral neuropathy. Because of its short plasma half-life it is normally given more than once daily, which creates an opportunity for a sustained-release oral formulation.

The present work develops six methylcobalamin matrix tablet formulations (F-1 to F-6) carrying 1.5 mg of drug per 300 mg uncoated tablet (306 mg after a 2 % film coat), in which the ratio of HPMC K-15M to HPMC K4M is varied. Wet granulation with PVP K-90 in isopropyl alcohol was followed by drying, milling and extra-granular blending with Aerosil 200, talc and magnesium stearate. Powder blends and compressed tablets were characterised for flow, mass uniformity, hardness, friability, drug content and in-vitro release in phosphate buffer pH 6.8 (USP type-I apparatus, 50 rpm) over 12 h. Optimised tablets were placed on 3-month accelerated stability at 40 °C / 75 % RH.

Drug-excipient compatibility was confirmed by FTIR. Hardness ranged from 1.57 to 3.57 kg/cm², friability stayed below 1 % for batches F-2 to F-6 and drug content lay within 99.66-100.26 %. Batch F-5 achieved the most favourable release profile, with 96.45 % of the label dose released over 12 h, and retained its appearance, drug content and release profile through 3 months of accelerated storage.

F-5, based on a balanced HPMC K-15M / HPMC K4M matrix, is therefore proposed as a sustained-release methylcobalamin candidate suitable for further pharmacokinetic evaluation.

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

INTRODUCTION

Oral drug delivery system

Oral administration is the preferred route for chronic drug therapy because it is convenient, well accepted by patients and adaptable to diverse dosage form designs. Immediate-release tablets produce fluctuating plasma concentrations and require repeated dosing, which weakens adherence and broadens the toxicity window. Sustained-release (SR) matrix tablets address this by maintaining therapeutic plasma levels for an extended interval from a single oral dose.[1–3]

Methylcobalamin is the natural cobalamin coenzyme used clinically to correct cobalamin (B12) deficits , most commonly pernicious anaemia and the peripheral neuropathy that can accompany it. Its relatively brief plasma residence means it is dispensed as an immediate-release tablet or as an injectable, both of which require frequent dosing; a 12-hour oral matrix would consolidate dosing and smooth plasma exposure.[4,5]

Hydroxypropyl methylcellulose grades K-15M and K4M are widely used hydrophilic polymers that hydrate on contact with aqueous fluids and form a swollen gel layer; drug release is then controlled by a combination of diffusion through this gel and erosion of the matrix. Their ratio can be tuned to deliver release over a targeted window.[6,7]

The present study formulates and evaluates six methylcobalamin SR matrix tablets that differ in the proportions of HPMC K-15M and HPMC K4M and characterises their pre-compression, post-compression, in-vitro release and short-term stability behaviour.

MATERIALS AND METHODS

MATERIALS

Methylcobalamin (1.5 mg per tablet) and all excipients used in this study, including HPMC K-15M, HPMC K4M (Methocel), microcrystalline cellulose, di-calcium phosphate (anhydrous), PVP K-90, isopropyl alcohol, talc, colloidal silicon dioxide (Aerosil 200), magnesium stearate and the Colorcoat FC4S-1 film-coating system, were of pharmacopoeial / laboratory grade and were used as received.

METHODOLOGY

Drug identification/Pre formulation studies

Drug identification and pre-formulation characterisation, comprising melting point determination, solubility screen, UV spectrophotometric calibration and FTIR analysis, were performed as summarised in Fig. 1.

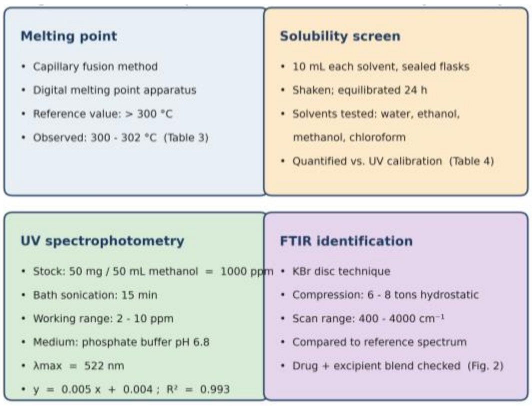

Fig. 1: Drug-identification and pre-formulation method summary for methylcobalamin.

Fabrication of tablets

Wet granulation produced the six methylcobalamin SR batches (coded F-1 PVP K-90 dissolved in isopropyl alcohol served as the granulating fluid; the wet mass was dried in a tray oven at 50 °C until loss on drying fell below 3 %, milled and re-sieved through #40 mesh to a uniform granule size. Extra-granular HPMC K-15M and HPMC K4M (the rate-controlling matrix polymers) were then sifted (#40) and blended with the granules for 15 min.
Aerosil 200 and talc (glidants) were added through F-6), each loaded with 1.5 mg of drug in a 300 mg uncoated core (306 mg after a 2 % Colorcoat FC4S-1 film coat).
at this stage. Magnesium stearate (lubricant) was sifted through #60, added last and blended for a further 3 min. The lubricated blend was compressed on a rotary tablet press to 300 mg per tablet and the cores were film-coated with Colorcoat FC4S-1 in dichloromethane / isopropyl alcohol to a final weight of 306 mg (2 % coating).

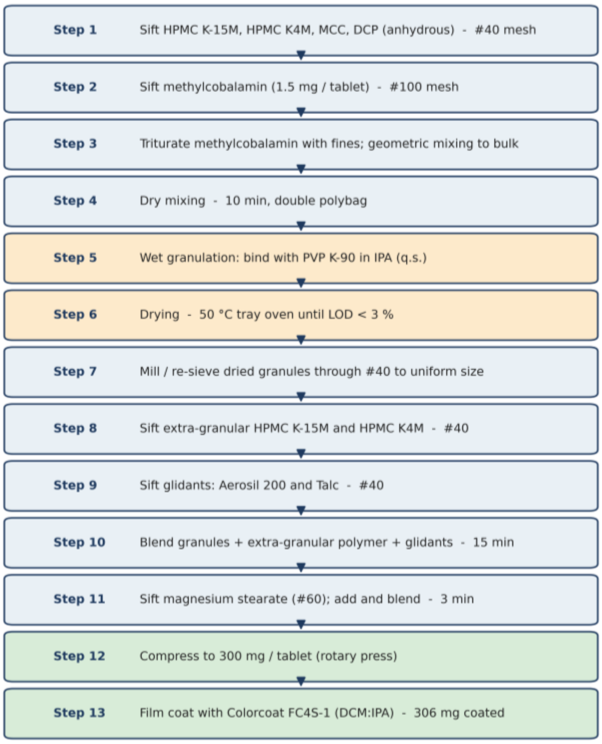

Fig. 2: Wet-granulation workflow for methylcobalamin sustained-release matrix tablets.

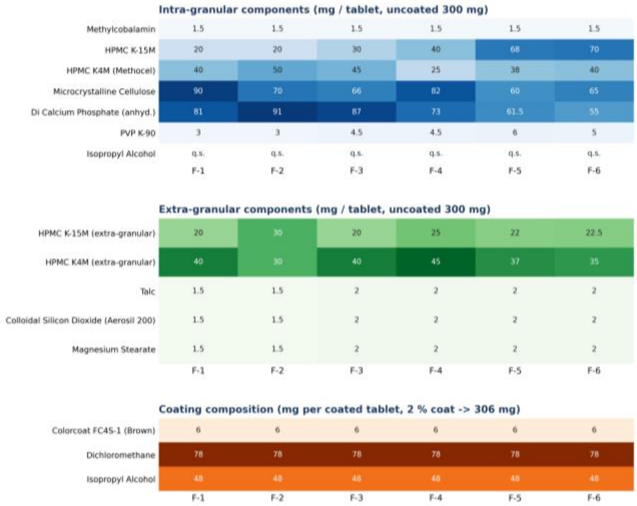

Fig. 3: Composition matrix (intra-granular, extra-granular and coating layers) for batches F-1 to F-6 of methylcobalamin SR tablets.

Evaluation parameters

Compressed tablets from every batch were assessed against the specifications summarised in Fig. 13, including mass uniformity, hardness, friability, thickness, percentage yield, angle of repose, in-vitro disintegration, in-vitro drug release, kinetic modelling and accelerated stability per ICH Q1A(R2).

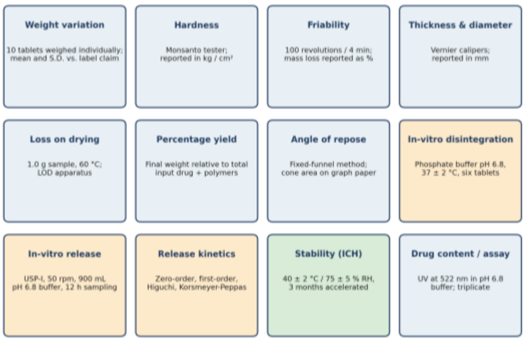

Fig. 4: Post-compression evaluation tests and target specifications applied to every batch.

RESULTS

Organoleptic Characteristics:-

Table 1: The Organoleptic Properties of Methylcobalamin

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

Table 2: 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

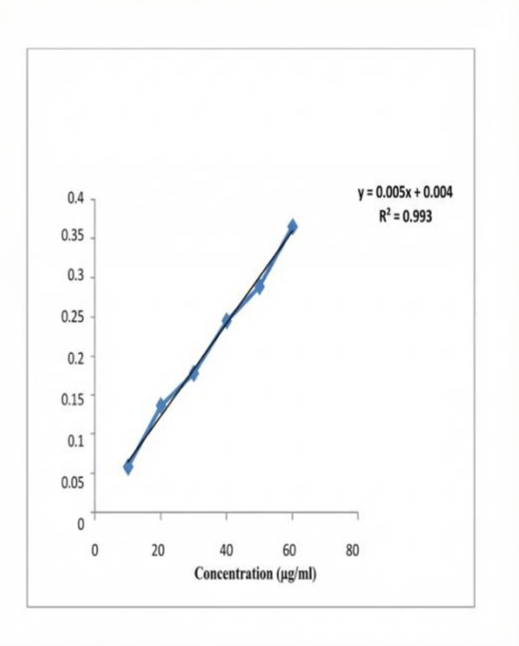

Fig. 5: Methylcobalamin calibration curve in phosphate buffer 6.8 pH at λmax-522 nm

Solution properties:

a) Solubility:

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

Table 3: Solubility study of Methylcobalamin

Sr. No.	Solvents and buffer	Results
1.	Acetonitrile	Partially soluble
2.	Ethanol	10 mg/ml
3.	Dimethyl sulfoxide	75 mg/ml
4.	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-

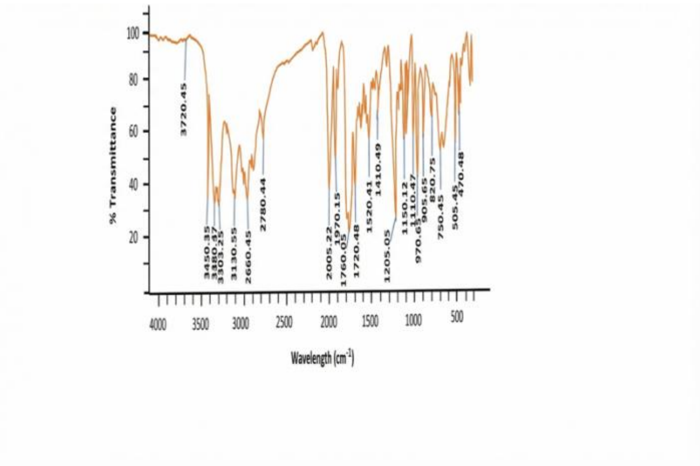

Fig. 6: FTIR Spectrum of Methylcobalamine (Sample)

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

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

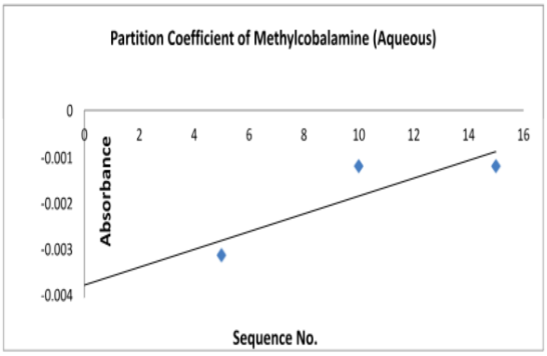

Fig. 7: Partition coefficient of methylcobalamin (aqueous)

OPTIMIZATION PRE-COMPRESSION PARAMETERS OF POWDER MIXTURE: -

Bulk Density: - (gm/ml.)

Table 4: 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.)

Table 5: 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.	303	306	308	310	300	303
9.	303	301	304	305	307	300
10.	300	304	303	304	306	307
Mean ± S.D.	**304 ± 2.55**	**304 ± 2.91**	**304 ± 2.95**	**304 ± 2.94**	**305 ± 2.58**	**304 ± 3.34**

Hardness: - (kg/cm^2)

Table 6: 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 7: % 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 %

A graphical summary of the post-compression results (bulk density, weight variation, hardness and drug content) across the six formulations is shown in Fig. 10, with the optimised batch F-5 highlighted.

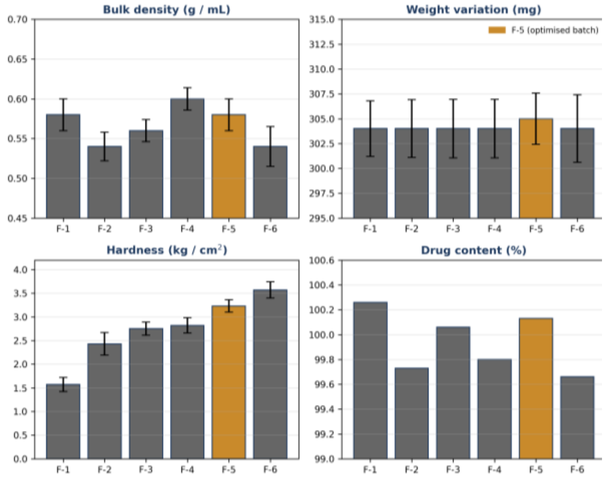

Fig. 8: Post-compression evaluation summary for the six methylcobalamin SR formulations.

IN-VITRO DRUG RELEASE STUDY: -

Cumulative drug release profiles for the six matrix formulations are shown in Fig. 9. Batch F-5 gave the highest cumulative release, reaching 96.45 % of the label dose at 12 h, while the remaining formulations released progressively less drug over the same interval.

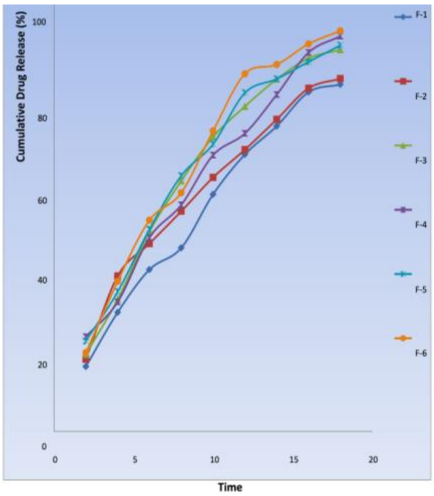

Fig. 9: Cumulative % Drug release Methylcobalamin Sustained Release Tablet, of all formulations.

Release Kinetic Analysis: -

In-vitro release data from the six batches were fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas models. The best-fit kinetic model for the optimised batch F-5 (highest R^2) is reported as best-fit model and R^2.

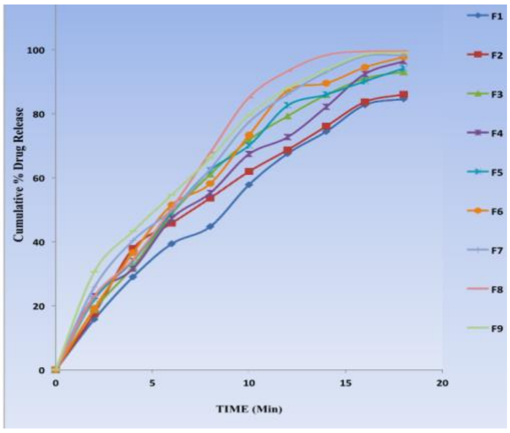

Fig. 10: Zero order release kinetic plot

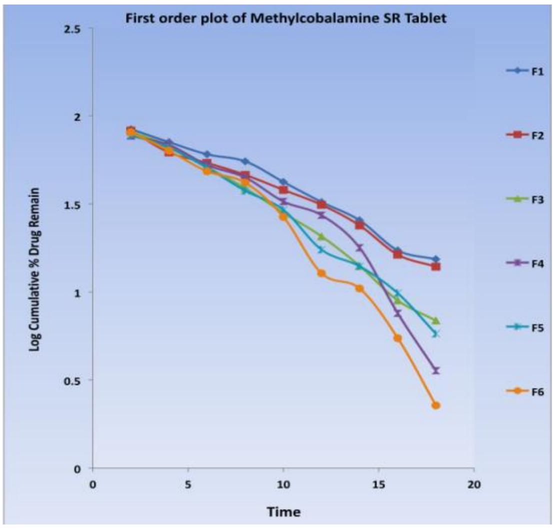

Fig. 11: First order release kinetic plot of Methylcobalamine Sustained Release Tablet.

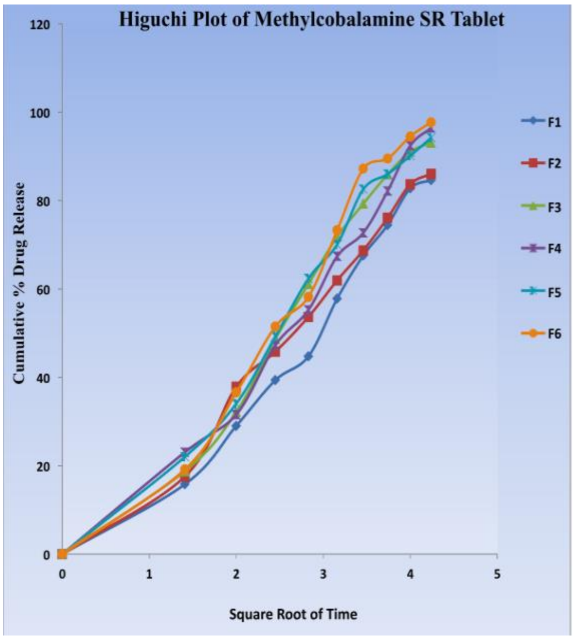

Fig. 12: Higuchi release kinetic plot of Methylcobalamine Sustained Release Tablet.

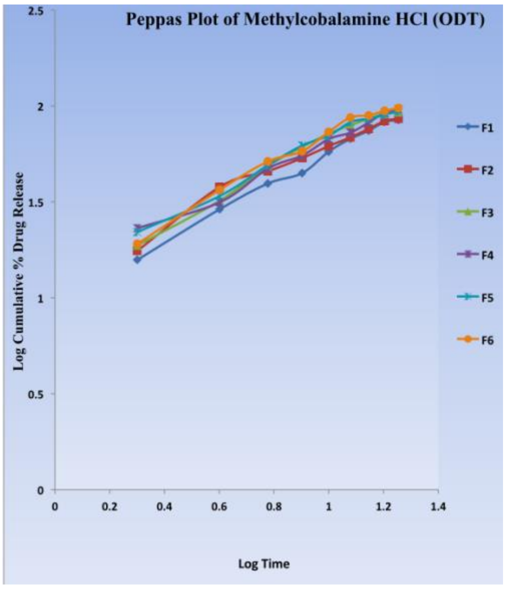

Fig. 13: Korsmeyer Peppas release kinetic plot of Methylcobalamine Sustained Release Tablet.

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:-

Three-month accelerated stability data for the optimised batch F-5 are summarised in Table 8.

Table 8: In-Vitro % Release Result of stability study of optimized formulation

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

FTIR spectra of pure methylcobalamin and of the final compressed blends showed no new absorption bands and no significant shift of existing peaks, indicating that the drug remained chemically compatible with the matrix excipients (Fig. 2).

Powder blends from all six matrices flowed acceptably prior to compression, with bulk density between 0.51 and 0.62 g/mL, tapped density between 0.55 and 0.70 g/mL and angles of repose in the free-flowing range. Compressed cores showed mean crushing strengths in the 1.6-3.6 kg/cm² interval and friability values that stayed below the 1 % pharmacopoeial limit from F-2 onwards (Tables 5-7). Assay values across the six batches lay between 99.66 % and 100.26 % of label claim (Table 8); the modest variability seen for F-2 and F-6 remains well within Indian Pharmacopoeia tolerances.

Three-month accelerated storage at 40 ± 2 °C and 75 ± 5 % RH preserved the appearance, drug content and release performance of F-5 (Table 9), supporting its short-term stability under stress conditions.

CONCLUSION

Among the six methylcobalamin sustained-release matrix tablets evaluated in this study, batch F-5 emerged as the optimised formulation, releasing 96.45 % of the label dose over 12 h. The balanced HPMC K-15M / HPMC K4M ratio in F-5 met all pharmacopoeial limits for hardness, friability, weight uniformity and drug content. Preservation of physical appearance, assay value and release profile after three months of accelerated storage supports F-5 as a viable candidate for subsequent pharmacokinetic and clinical evaluation.

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