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ORIGINAL ARTICLE

Formulation and *In-Vitro* Evaluation of Sustained Release Tablet of Isoniazid by Using Natural and Synthetic Polymers

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ABSTRACT

The objective is to create and assess isoniazid extended-release tablets using natural and synthetic materials (e.g. Eudragit L100, xanthan gum guar gum, and HPMC K100M). This project aims to analyze the performance of different polymers in terms of hardness, friability, chemical composition, and release rate. Tablets will be formed using different chemicals for various polymers and the compositions' chemical and physical characteristics will be evaluated. This research will also look at how the volume composition affects the dissolution rate of isoniazid. We will evaluate the formulation in terms of hardness, weight change, and drug content; Studies conducted in vivo and in vitro will be utilized to ascertain the stability of the formulation and the drug release profile. The results of this study will provide important information about the use of natural and synthetic products with the extended-release drug isoniazid, which is an important drug in the treatment of the disease. This study will also investigate how the chemical composition affects the isolation rate of isoniazid. Damage studies are important in determining the release rate from the drug and evaluating its bioavailability. The research will provide ideas about the components to be recommended to achieve the beneficial release of isoniazid by differentiating from the drug to the polymer. Finally, this study develops and evaluates isoniazid sustained release formulations using guar gum, xanthan gum, and Eudragit L100 as natural and synthetic polymers. This study will shed light on the composition of synthetic and natural polymers in sustained-release tablets of isoniazid, an important drug in treating tuberculosis.

Keywords: *Isoniazid, sustained release, natural polymers, synthetic polymers, in-vitro dissolution.*

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INTRODUCTION

Sustained-release drug delivery systems (SRDDS) release medication at a predetermined rate while maintaining constant drug levels over some time. This technology is designed to improve drug delivery by providing effective treatment and detoxifying the blood. Oral medication delivery is frequently regarded as the most widely used and practical approach. Advances in manufacturing technology have been beneficial when compared to modified-release and delayed-release oral materials for established models. SRDDS can improve patient compliance and bioavailability by providing more sustained drug release. Due to its short shelf life, SRDDS is particularly suitable for drugs that must be taken frequently [1] Reservoir release, controlled release, prolonged release, sustained release, and sustained release are some of the names given to drug delivery systems designed to release the medication slowly after a single dose and provide long-term clinical benefits. The main objective of developing a sustained release system is to reduce the required dose, ensure consistent dosing, reduce its frequency, or increase the potency of the drug by providing drug delivery to the office. First of all, the best delivery method should be taken just once for the course of the therapy, whether it be a few days or a week. (depending on the disease information), or the patient's life (diseases such as diabetes, and high blood pressure). Second, it should send supplies directly to the workplace to reduce the possibility of adverse outcomes [2,3]. To achieve unprecedented changes in the *in vivo* setting in which medication distribution takes place, to improve drug delivery, and to achieve certain controlled clinical results, the system standard release drug is

designed to maintain blood levels over a long period. This system is designed to deliver a dose that will produce a therapeutic effect over time. Drugs with short half-lives that require repeated administration benefit greatly from the release of drug delivery [4]. The balance of benefits and drawbacks shows that sustained-release drug delivery methods are intended for improvement in medication therapy. This method has many advantages over conventional medicine, such as reducing the frequency, reducing regular drug changes, using more drugs, improving drug safety, reducing treatment changes, treatment costs depending on the improvement, and reducing the duration of treatment [5,6]. Sustained-release Drug delivery systems can provide zero-order release, whereby the medication is made available over time regardless of concentration. Such release is possible. In contrast, sustained release refers to the gradual release of a drug over time, which may or may not be controlled release [7,8]. Drug delivery systems with sustained release are created to maintain blood pressure over an extended period, thus providing optimal drug delivery and some therapeutic control even in a setting where drug use in vivo has an unavoidable effect. Higher patient compliance, fewer changes in steady-state medications, more effective drug use, shorter treatment times, better therapy leading to lower healthcare expenditures, and safer use of drugs with greater strength duration are just a few of the many benefits these systems offer over conventional medicine. [9,10]

MATERIAL AND METHODS

Materials

Isoniazid, Xanthan gum, Guar gum, Eudragit L100, HPMC K100 M, Microcrystalline cellulose, Lactose, Lactose, Magnesium stearate, Talc.

Formulation of Sustained Release Tablet by Direct Compression Method:

1. Collect isoniazid, polymer (xanthan gum/guar gum/Eudragit L100/HPMC K100M), microcrystalline ce llulose (MCC), lactose, magnesium stearate, and talc one by one through a 1.60 sieve.
2. Isoniazid, (Xanthan gum/ Guar gum/ Eudragit L100/ HPMC K100M) and Lactose were carefully triturated using a mortar and pestle to create a homogenous mixture.
3. After the trituration mixer was placed in an RMG (Rapid Mixer Granulator) for 30 mins at 150 rpm.
4. Finally, after adding the talc and magnesium stearate, mixing was carried out for a further five minutes.
5. Using a 10 mm punch on a ten station "B" Tooling Rotatory Tablet Punching Machine, the substance and excipient solution were crushed to create convex-faced tablets with a weight of 300 mg apiece. [11,12]

Formulation strategy: Details of Ingredients and quantity mentioned below in table**:**

Sr.no.	Ingredients	Quantity (mg)							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	Isoniazid	100	100	100	100	100	100	100	100
2.	Xanthan gum	60	60	75	75	-	-	-	-
3.	Guar gum	-	-	-	-	60	60	75	75
4.	Eudragit L100	-	-	-	-	-	-	-	-
5.	HPMC K100 M	-	-	-	-	-	-	-	-
6.	Microcrystalline cellulose	45	60	45	60	45	60	45	60
7.	Lactose	80	65	65	50	80	65	65	50
8.	Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
9.	Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight of the tablet		300 mg.							

Sr.no.	Ingredients	Quantity (mg)							
		F9	F10	F11	F12	F13	F14	F15	F16
1.	Isoniazid	100	100	100	100	100	100	100	100
2.	Xanthan gum	-	-	-	-	-	-	-	-
3.	Guar gum	-	-	-	-	-	-	-	-
4.	Eudragit L100	45	45	60	60	-	-	-	-
5.	HPMC K100 M	-	-	-		45	45	60	60
6.	Microcrystalline cellulose	45	60	45	60	45	60	45	60
7.	Lactose	95	80	80	65	95	80	80	65
8.	Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
9.	Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight of the tablet		300 mg.							

Evaluation procedures:

1)Pre-compression Parameter:

Bulk Density

The quantity of loose powder per unit volume, including the space between the particles, is known as bulk density or apparent density. particles, the volume & the envelop volume of the particles.

Tapped Density

The prohibited density obtained after "tapping" is called the "tapped density apparatus." The gadget typically raises and lowers a volumetric measuring cylinder dragging the powder mix from an initial distance.

Flow Properties

API and excipient flow evaluations are done to make sure that the particles will pass through equipment used for processing like a tablet press, hopper, or compactor with acceptable flow.

Compressibility index (C.I.):

It is a measurement of a powder's tendency to solidify. It is an assessment of the interaction between particles in a free-flowing powder; in general, the form of contact is not as important and the BD and TD values will be near. bigger inter-particle contact is usually the outcome of poor flowing material; bridging between particles commonly results in a lower bulk density and a bigger difference between BD and TD, which difference shows up in the compressibility index.

Hausner's ratio:

A metric called Hausner's ratio is used to express how compressible powder is. It was the tapped density divided by the bulk density. The formula is used to compute it.

$$\textbf{Hausner's Ratio} = \rho t/\rho b$$

The angle of Repose:

The angle of repose is a property linked to interarticular opposition to particle motion or friction. Calculating the frictional forces in a loose powder may be done using the angle of repose. A mound of powder can only angle with the horizontal plane to this maximum degree. The coefficient of friction (μ) among the particles is equivalent to the tangent of the angle of repose. [13,14].

2) Post Compression Parameters

Physical appearance:

The core tablet's appearance, including any visible fractures, surface roughness, and chipping.

Thickness and diameter:

During compression, the diameter and thickness of the tablets were measured with vernier calipers.

Hardness:

The Monsanto hardness tester was used to measure the tablet's hardness for each formulation. The tablet was positioned between the tester's two jaws along its oblong axis. The value ought to be 0 kg/cm^2 at this stage. The knob was rotated to apply a continuous force until the tablet broke. At this stage, the value was expressed in kilograms per cubic meter.

Friability:

The factors that cause tablets to chip, cap, or shatter are friction and shock. The friability test is linked to tablet hardness and is used to assess a tablet's ability to tolerate abrasion during packing, handling, and shipping. The Roche Friabilator was used to measure it.

Drug content:
To find the average weight, 20 pills were weighed and then coarsely ground in a mortar. After precisely weighing and transferring the powered mass to a 10 ml volumetric flask, 10 milligrams of isoniazid was present. The mixture was sonicated for fifteen minutes after the solvent (phosphate buffer 6.8 pH) was added to the volume. Using a 0.45µm nylon filter, an aliquot was filtered. After diluting the final tablet solution with a solvent (phosphate buffer 6.8 pH) to a concentration of 10 µg/ml, the UV at 263 nm was used to examine the results. for determination of drug content.

Weight Variation:
An electronic balance was used to weigh 20 tablets of each formulation in order to examine weight variance, and the standard protocol was followed throughout the test. IP & USP specify that no tablet shall vary by more than twice the applicable amount, and that no two tablets' average weights should fluctuate by more than the percentages indicated.[15]

Dissolution time:
USP apparatus type II was used to conduct in-vitro dissolving investigations at 100 rpm for sustained-release isoniazid tablets. 0.1 N hydrochloric acid (900 ml) was the dissolving media used for the first two hours, and thereafter phosphate buffer 6.8 pH was employed. solution (900ml) was used as dissolution medium for up to 10 hrs. (3 – 10) and maintained at $37^0C \pm 0.5^0C$.

RESULTS AND DISCUSSION

1) Preformulation study:

A. Physical examination
The acquired drug samples' drug characterisation characteristics, such as color, odor, and appearance, were examined; the findings are displayed in Table 1.

Table 1: Drug characterization parameters

Color	White
Odor	Odourless
Appearance	Fine powder

B. Determination of melting point:
It was discovered that isoniazid's melting point fell between 170-172 ℃ which complies with the reported melting point of Isoniazid.

C. Solubility study:
Several solvent systems were used to conduct the isoniazid solubility investigation in accordance with the literature. The findings of solubility are displayed in Table 2.

Table 2: Results of the solubility study

Sr.no	Solvent	Observation
1.	Methanol	Soluble
2.	Phosphate buffer 6.8 pH	Soluble
3.	0.1 N Hydrochloric acid	Soluble
4.	Water	Insoluble

D. UV-visible spectrophotometric analysis:
Preparation of Calibration curve for Isoniazid:

1) Preparation of Calibration curve for Isoniazid in 0.1 N Hydrochloric acid:
The absorbance of various concentrations in 0.1N hydrochloric acid at 266 nm was measured in order to create the isoniazid calibration curve. Table 3 display the calibration curve that was developed.

Table 3: Result of Calibration curve for Isoniazid in 0.1N Hydrochloric acid

Sr.no.	Concentration (ppm)	Absorbance
1.	5	0.1859
2.	10	0.3568
3.	15	0.5694
4.	20	0.7439
5.	25	0.9541

The calibration curves were linear and obeyed in the concentration range of 5-25 µg/ml, Beer-Lambert's law applies. The results of the correlation coefficient were 0.9988. indicating excellent linearity of the data.

2) Preparation of Calibration curve for Isoniazid in Phosphate buffer 6.8 pH:

The absorbance of various concentrations in phosphate buffer 6.8 pH at 263 nm was measured in order to create the isoniazid calibration curve. The acquired calibration curve may be seen in Table 4 .

Table 4: Result of Calibration curve for Isoniazid in Phosphate buffer 6.8 pH

Sr.no.	Concentration (ppm)	Absorbance
1.	5	0.1587
2.	10	0.3265
3.	15	0.4516
4.	20	0.6471
5.	25	0.8145

The calibration curves were linear and fulfilled the concentration range of 5–25 µg/ml according to Beer–Lambert's law. There was a correlation coefficient of 0.9962. indicating excellent linearity of the data.

E. FT-IR of Isoniazid:

An FTIR spectrometer was used to record Isoniazid's infrared spectrum. In Figure 1, IR spectra are displayed. The FTIR spectrum revealed distinctive functional groups, as seen in Table 5.

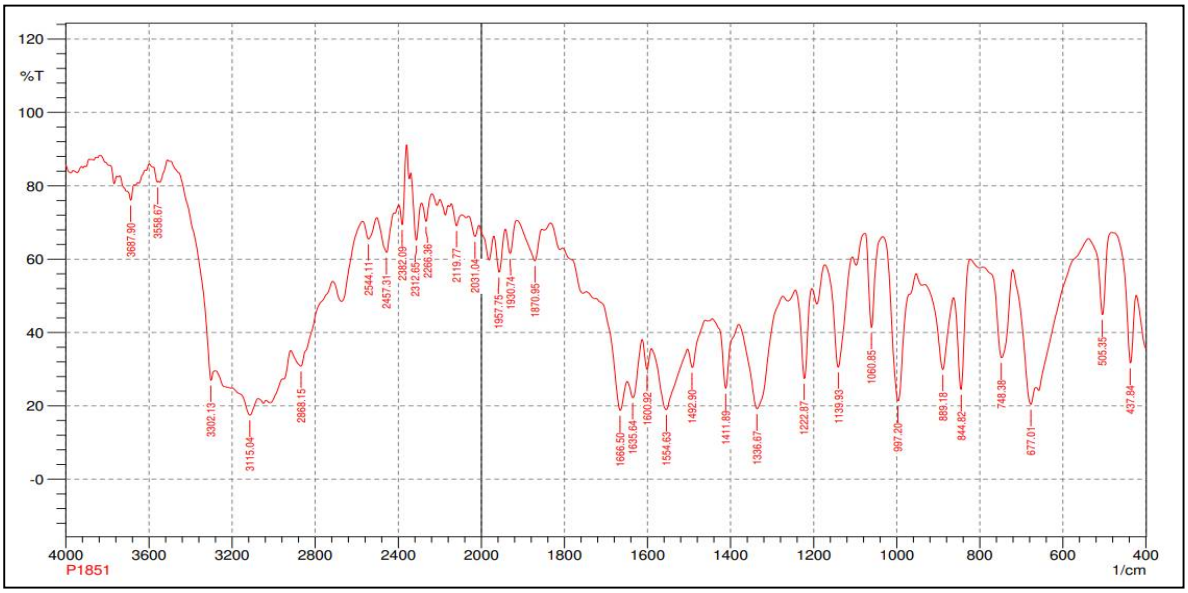

Figure 1: IR of Isoniazid

Table 5: IR frequencies of Isoniazid functional group

Functional group	Observed Frequency	Reported Frequency
N-H stretching (Aliphatic primary amine)	3302.13	3400-3300
C-H stretching (Aromatic group)	2868.15	3000-2800
C=O stretching (Acid halide)	1870.95	1870-1785
C=C stretching (aromatic amine)	1336.67	1342-1266
C-N stretching (Amide group)	1492.9	1500-1400

Drug excipient compatibility study:

There was no interaction between the medication, polymer, and excipients, according to the observation of the FTIR Spectra of isoniazid in both its pure form and its physical combination. The compatibility study's IR spectra and their respective functional group detection data are shown in Table 6.

Table 6: Result of Drug excipient compatibility

Ingredient	Ratio	Initial	Condition
			40°C/75% RH (Accelerated)
			1 month
Isoniazid	NA	White	NCC
Isoniazid: Xanthan gum	1:1	Off White	NCC
Isoniazid: Guar gum	1:1	Off White	NCC
Isoniazid: Eudragit L100	1:1	White	NCC
Isoniazid: HPMC K100M	1:1	White	NCC
Isoniazid: MCC	1:1	White	NCC
Isoniazid: Lactose	1:1	White	NCC
Isoniazid: Magnesium stearate	1:1	White	NCC
Isoniazid: Talc	1:1	White	NCC

Note: RH (Relative Humidity) and NCC (No Conformational Change) in physical appearance from the original description.

The aforementioned data shows that the isoniazid combination was stable when all of the development and formulation excipients were employed.

2) Post compression parameters:

A. Physical appearance:

Round, convex tablets with beveled edges and upper and lower surfaces were either white or off-white in color throughout all sample batches.

B. Thickness and diameter:

Using a Vernier caliper and selecting the tablets at random, the thickness and diameter of each tablet were measured. Table 10 displays the average values. The values in every formulation are essentially the same. The diameter was discovered to be between 9.4 and 9.6 mm, while the thickness ranged from 4.8 to 5.1 mm, respectively. The consistency of the data demonstrates that the formulations were crushed without sticking to the dies and punches.

C. Hardness:

All of the batches' hardness values were determined using a Monsanto hardness tester, and the findings are shown in Table 10. It was discovered that hardness ranged from 7.5 kg/cm2 to 9.5 kg/cm2. All of the formed batches had consistent hardness and strong mechanical strength in addition to enough hardness.

D. Friability:

Using the Roche Friabilator, tablets from all batches were assessed. The friability of the tablets was found to be within the permissible range of 0.25 to 0.81 (less than 1%). Table 10 displays the outcome.

Table 10: Result of Post-compression parameters

Batches	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
F1	5.0±0.1	9.5±0.1	7.5±0.5	0.81
F2	4.9±0.2	9.6±0.2	8±0.5	0.63
F3	5.0±0.2	9.5±0.1	8±0.5	0.58
F4	4.9±0.3	9.6±0.1	8.5±0.5	0.48
F5	4.9±0.2	9.6±0.2	8±0.5	0.49
F6	4.9±0.2	9.5±0.2	8.5±0.5	0.38
F7	5.0±0.1	9.4±0.2	8.5±0.5	0.29
F8	5.1±0.3	9.4±0.2	9±0.5	0.26
F9	4.9±0.2	9.6±0.2	8±0.5	0.39
F10	4.8±0.1	9.6±0.1	8.5±0.5	0.58
F11	4.9±0.2	9.6±0.2	8.5±0.5	0.47
F12	4.9±0.2	9.5±0.1	9±0.5	0.29
F13	5.0±0.1	9.5±0.1	9±0.5	0.32
F14	5.0±0.2	9.4±0.2	9.5±0.5	0.32
F15	4.9±0.2	9.6±0.2	9±0.5	0.25
F16	5.0±0.1	9.4±0.2	9.5±0.5	0.28

E. Drug content:

Every formulated batch underwent a drug content uniformity test, the results of which are shown in Table 11. The drug concentration was discovered to be between 98% and 102%, which was less than the allowed amount.

Table 11: Result of Drug content

Batches	Drug content
F1	100.30
F2	98.18
F3	100.91
F4	99.09
F5	100.61
F6	99.30
F7	98.82
F8	101.52
F9	99.65
F10	98.56
F11	100.36
F12	98.99
F13	99.55
F14	99.60
F15	100.67
F16	100.92

F. Weight Variation:

Direct compression was the method used to make the tablets. Due to the material's unrestricted flow, homogeneous die filling resulted in tablets with consistent weight. According to pharmacopeia criteria, all manufactured batches of tablets had weight fluctuations that were within an acceptable range, meaning that they were less than 5%. Table 12 provides the results.

Table 12: Result of Weight variation results

Batches	Weight variation	
	Weight (mg) ± S. D	Weight variation (5 %)
F1	305 ± 2	Passes
F2	300 ± 5	Passes
F3	305 ± 4	Passes
F4	295 ± 3	Passes
F5	298 ± 5	Passes
F6	302 ± 5	Passes
F7	294 ± 6	Passes
F8	299 ± 4	Passes
F9	303 ± 6	Passes
F10	308 ± 5	Passes
F11	299 ± 3	Passes
F12	298 ± 6	Passes
F13	304 ± 5	Passes
F14	303 ± 4	Passes
F15	296 ± 3	Passes
F16	298 ± 6	Passes

G. In vitro dissolution test:

Using 0.1N hydrochloric acid (0–2 hours) and phosphate buffer 6.8 pH (3–10 hours) as the dissolving media, the in vitro assessment of each prepared batch lasted for 10 hours. The percentage CDR was calculated using the corresponding equation of a line. The results are expressed in Tables 13, 14, and figure 2.

Batches prepared by using natural as well as synthetic polymers and a low concentration of binding agent failed to maintain the medication's release for up to 10hrs whereas batches prepared by using natural as well as synthetic polymers and a high concentration of binding agent sustained the drug release up to 10hrs. Maximum drug release after 10 hrs was found in the F12 batch at 99.16%.

Table 13: Result of In-vitro dissolution

Time (hrs.)	Batches	% Cumulative Drug Release (%)							
		F1	F2	F3	F4	F5	F6	F7	F8
1		18.46	15.58	14.45	15.67	14.45	15.68	15.28	14.53
2		32.27	26.14	26.69	27.37	25.69	25.16	28.16	25.77
3		50.79	40.68	39.04	39.26	39.24	40.05	41.05	38.32
4		69.78	58.78	51.27	51.57	55.27	54.06	53.36	51.35
5		82.45	76.58	62.59	65.99	77.39	65.78	62.78	64.47
6		94.28	85.46	73.13	73.49	88.13	76.28	74.28	72.21
7		95.18	92.92	83.64	81.27	91.34	85.06	82.06	80.42
8		-	94.06	89.55	87.37	93.68	93.61	89.13	86.06
9		-	-	96.36	93.12	-	97.36	96.55	92.43
10		-	-	-	98.55	-	-	-	96.4

Time (hrs.)	Batches	% Cumulative Drug Release (%)							
		F9	F10	F11	F12	F13	F14	F15	F16
1		19.75	19.02	19.34	15.67	14.75	14.53	13.74	12.81
2		35.15	32.96	34.02	27.37	25.99	25.77	24.52	23.72
3		49.76	49.58	50.04	39.26	39.54	38.32	37.71	36.03
4		62.09	59.92	60.58	51.57	50.57	51.35	50.82	46.08
5		74.61	71.06	72.12	65.99	62.69	64.47	61.64	55.52
6		85.75	83.36	82.22	73.49	71.43	72.21	71.14	65.61
7		95.25	91.05	89.61	81.27	79.64	80.42	77.61	75.03
8		95.95	93.85	94.08	87.37	86.98	86.06	82.72	81.43
9		-	95.92	95.79	93.12	92.66	92.43	94.72	86.52
10		-	-	96.63	99.15	-	96.4	-	89.71

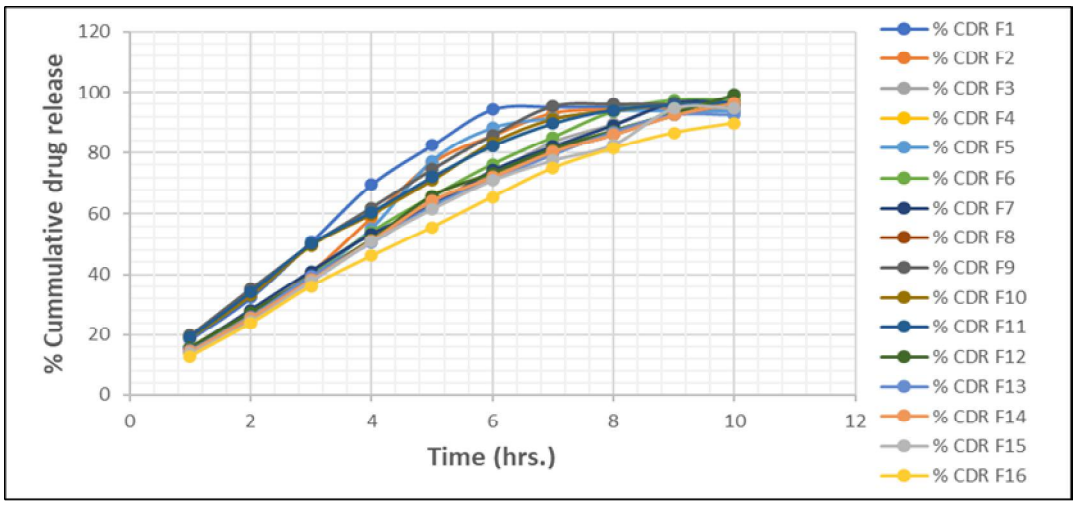

Figure 2: In vitro dissolution study

CONCLUSION

Based on information gathered from batches' pre- and post-compression assessments as well as in vitro dissolution study F12 (Eudragit L100 20% and MCC 20%) was selected as the optimized batch.

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