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FORMULATION OPTIMIZATION AND INVITRO EVALUVATION OF NIACIN PROLONGED RELEASE TABLET

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ABSTRACT

The objective of the present research work is to develop a pharmaceutically stable, cost effective and quality improved formulation of "Niacin prolonged release matrix tablets" which is to be bioequivalent with reference product. For the preparation of niacin prolonged release tablets both direct compression and wet granulation method using various polymers such as Methocel K100M, Methocel E15LV, Pharmatose 200M, Cutina HR, Pamster and aerosol. Wet granulation method was carried out in fluidized bed processor with optimized parameters. Tablets were prepared and evaluated for thickness, hardness, friability, weight variation, content uniformity, and *in vitro* drug release. For the entire formulations similarity factor and dissimilarity factors were calculated among all these results formulation 8 values are satisfied. The release kinetics of the drug was observed to fit best with korsmeyer peppas having regression coefficient of linear line as 0.999 and slope was 0.65. The bottles are loaded in accelerated stability chambers at 40^0C / 75 % RH conditions. Samples were analysed after one month and two months intervals.

KEYWORDS: prolonged release tablets, Niacin, Polymers.

INTRODUCTION

Oral drug delivery is the most convenient route of administration because of ease of compliance, greatest stability, accurate dosage and ease of manufacturing. Prolonged release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a extended period of time after administration of a single dose. niacin is an antihyper lipedimic used for the treatment of hyperlipidemia which is available as immediate release and sustained release tablets In those immediate release formulations which are available in market causes cutaneous flushing.

MATERIALS AND METHOD

Niacin was gifted by the cipla company colloidal silicon dioxide is from chemo labs hydroxypropyl methyl cellulose is gifted by the Darwin company hydrogenated castor oil and hydroxy propyl metyhl cellulose was gifted by loba chemie Pvt. Ltd, Mumbai.

METHOD OF PREPARATION

Niacin methocel k100, Lubritab and aerosil. All thes are sifting under mesh and mix in polybag and mix and methoceleE15 LV in purified water and granulation takes place in fluidized bed process process by maintaining 35-59^0 after that granulating take place by fluidized bed process and again presifting with magnesium stearate

with 40mesh and 3 minites lubrication was done in 3 liters multi attached blender and the compress20*105mm modified capsule shape.

In Vitro Drug Release Studies

The formulated matrix tablets were tested using the USP Apparatus II (paddle type) in 900 mL of 0.1N HCl as the dissolution medium. The test was conducted at a paddle speed of 75 rpm and a controlled temperature of 37°C ± 0.5°C.

Samples (5 mL) were withdrawn at six predetermined time points: 1st, 3rd, 6th, 9th, 12th, and 20th hour, over a 20-hour period. Each sample was centrifuged, appropriately diluted, and analyzed using a UV spectrophotometer (Shimadzu UV-1650 PC) at a wavelength of 263 nm. After each sampling, an equal volume (5 mL) of fresh dissolution medium, maintained at the same temperature, was added to replace the withdrawn volume. All experiments were performed in triplicate, and the results were reported as average values.

Evaluation of Prepared Matrix Tablets

The prepared matrix tablets were subjected to various evaluation parameters including hardness, weight variation, thickness, friability, and drug content. Hardness was measured using a Strong-Cobb hardness tester. Friability was assessed using a Roche friabilator (Campbell Electronics, Mumbai). Thickness was determined using vernier calipers. Weight variation was evaluated as per the official method described in the *British Pharmacopoeia*.

Evaluation of Physical Characteristics

Evaluation of Prepared Matrix Tablets

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Evaluvation of physical test

Table 1

Formulation no	Average thickness	hardness	Average weight	Weight variation
F1	8.5	10-10	1270.0	1268-1274
F2	8.2	10-11	1275.5	1262-1278
F3	7.5	19-20	1422.4	1410-1429
F4	7.2	20-21	1416.0	1410-1425
F5	7.7	19-21	1360.0	1356-1363
F6	7.0	18-20	1331.5	1326-1334
	F7	18-20	1373.5	1369-1376
F8	7.5	21-22	1360.0	1356-1363

ACCELRATED STABILITY TEST

Table 2

S. NO	Test	Specifications	Initial	After 1 month	After 2 months
1	Description	White crystalline powder	Complies	Complies	Complies
2	Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay	Complies	Complies	Complies
3	Dissolution in water	NLT 85% release after 24 hours	Complies	Complies	Complies
4	Related substance	NMT 0.5%	Complies	Complies	Complies

Among all the formulations, formulation 8 was given good results as best formulation. Formulation 8 tablets were evaluated for accelerated stability studies at 40^0C / 75 % RH condition. The stability details / results are presented as below.

- Storage Condition: 40^0C / 75 % RH
- Pack: HDPE Container
- Storage Period: 1 month and 2 months

Release Kinetics

Study of Release Kinetics

In vitro dissolution has been recognized as an important release element in drug development.

Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. The quantitative interpretation of the values obtained in the dissolution assay is facilitated the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms. To compare dissolution profiles between two drug products model dependent (curve fitting), statistic analysis and model independent methods can be used. The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable (e.g. time) are mentioned below. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like R^2 value.

Zero order kinetics*:* Assumption*:* Drug dissolution is from a pharmaceutical dosage forms that does not disaggregate and releases the drug slowly (assuming that area does not change and no equilibrium conditions are obtained).

The equation describing the kinetics is depicted in equation 3.

$Q_o = Q_t + K_o t$ *Eq* (3)

Where,
Q_t is the initial amount of drug dissolved at time t,
Q_o is the initial amount of drug in the solution, most of the times it is equal to zero,
K_o is the zero order release rate constant.

Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a sustained release product

First order kinetics: The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman in 1967.

Equation:

$$Q_t = Q_0 e^{-K_1 t} \quad \text{or} \quad \ln\left(\frac{Q_t}{Q_0}\right) = K_1 t \quad \text{or} \quad \ln q_t = \ln Q_0 K_1 t$$ *Eq* (4)

or in logarithm

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303}$$ *Eq* (5)

Where,
Q_t is the initial amount of drug dissolved at time t,
Q_o is the initial amount of drug in the solution,
K_1 is the first order release rate constant

In this way a graphic of the decimal log of the released amount of drug vs time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in the porous matrices would release the drug in a way that is proportional to the amount of drug remaining in its interior.

Higuchi model: This model was first proposed by Higuchi, 1961 to describedissolution of drug in suspension from ointment bases, but is widely applicable to other types of dosage forms]. The Equation describing release*:*

$$f_t = Q = \sqrt{D(2C - C_s)C_s t}$$ *Eq* (6)

Where,
Q is the amount of drug released at time t per unit area,
C is the initial concentration,
C_s is the drug solubility in matrix media,
D is the diffusivity of the drug molecule (Diffusion Constant) in the matrix substance. The above equation is based on the assumptions that the initial drug concentration in the system is much higher than the solubility of drug. This assumption is very important because it provides the basis for the justification for the applied pseudo steady state approach. The suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the system. Swelling or dissolution of the polymer carrier is negligible. The diffusivity of the drug is constant and perfect sink conditions are maintained.

Simplified Higuchi model

$$f_t = K_H t^{1/2}$$ Eq (7)

Where,
K_H is the Higuchi dissolution constant,
It describes drug release as a function of square root of time that is dependent on diffusion process based on Fick‟s Law.

1.7.3.4. Hixson Crowell model: Hixson and Crowell model recognizing that the particle regular area is proportional to the cubic root of its volume [45].

Equation

$$W_0^{1/3} - W_t^{1/3} = K_s t$$ *Eq* (8)

Where,
W_0 is the initial amount of drug in the pharmaceutical dosage form,
W_t is the remaining amount of drug in dosage form at time t, K_s is the constant relating surface volume ratio.

This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

Simplified equation:

$$(1-f_t)^{1/3} = 1 - K_\beta t \qquad Eq\ (9)$$

Where,
ft = 1-(Wt / W_0), represents drug dissolved fraction at time t,
K_β is the release constant.

A graph of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time.

It is assumed that the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through the polymeric matrix.

Korsmeyer- Peppas model: For prediction of mechanism of drug release through polymeric system korsmeyer and peppas, in 1983 developed a mathematical equation, relating exponentially the drug released to the elapsed time. It is a simple semi empirical equation also called as power law.

$Mt / M\infty = Kt^n$

Where,
M and M_∞ are the absolute cumulative amount of drug released at time t and infinite time,
k is a constant incorporating structural and geometric characteristics of the device,
n is the drug release exponent, indicative of the mechanism of drug release.

In Vitro Release Kinetics: To quality improved formulation of extended release matrix formulations containing 1000 mg of niacin having a comparative *invitro* dissolution profile with the innovator product.by using data analysis of release profile according to different kinetic models The drug releases from tablets were found slow and extended over 20 hours. The initial formulation of niacin tablets were formulated with, methocelk100, aerosil, methocelELV with different concentration.

PREPARATION OF NIACIN TABLETS BYWET GRANULATION METHOD

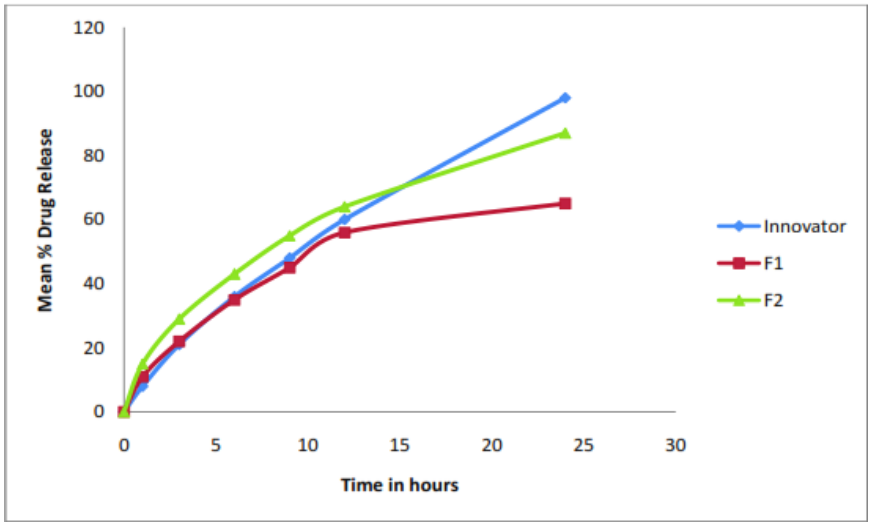
Table 3

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Niacin	1000	1000	1000	1000	1000	1000	1000	1000
Methocel K100 M	110.0	80.0	45.0	45.0	45.0	45.0	45.0	80
Cutina HR	165.0	162.0	164.0	164.0	164.0	163.6	162.0	164.0
Pharmatose 200 M	72.0	66.0	60.0	71.0	70.1	74.1	71.0	72.0
Aerosil	0.0	27.0	0	27.0	0	0	27.0	27.0
Cutina HR	0	15.0	0	15.0	0	15.0	15.0	15.01
Magnesium Stearate	12.0	0.0	0.0	15.01	5.0	0.0	15.0	15.0
Total weight(mg)	1359	1284	1337.01	1337.01	1284.1	1312.7	1807	1418.01

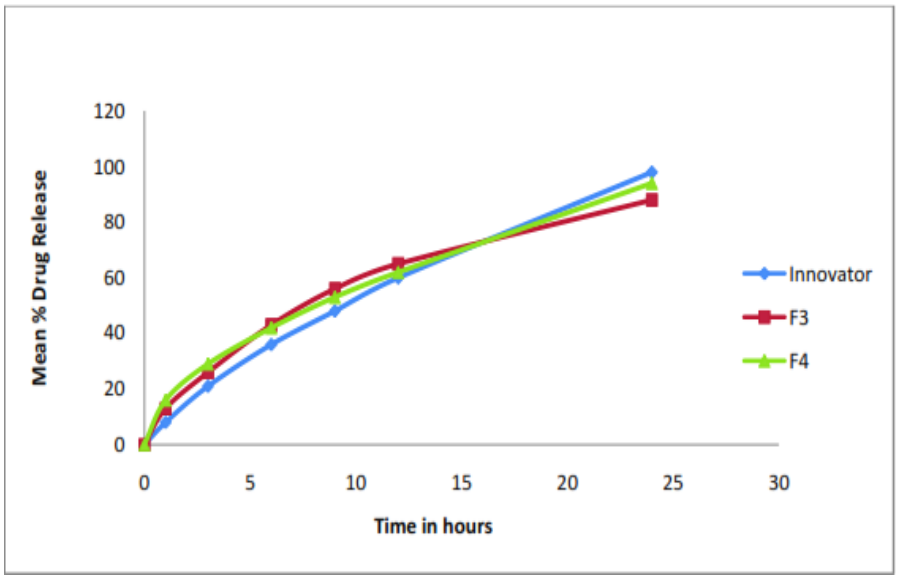
Table 4

Time in hr		**% PERCENT CELL DISSOLVED**							
	Innovator	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	**8**	**11**	**15**	**13**	**16**	**13**	**13**	**15**	**14**
3	**21**	**22**	**29**	**26**	**29**	**27**	**26**	**29**	**26**
6	**36**	**35**	**43**	**43**	**42**	**42**	**43**	**43**	**41**
9	**48**	**45**	**55**	**56**	**53**	**56**	**56**	**56**	**52**
12	**60**	**56**	**64**	**65**	**62**	**66**	**65**	**66**	**62**
24	**98**	**65**	**87**	**88**	**94**	**90**	**88**	**95**	**96**

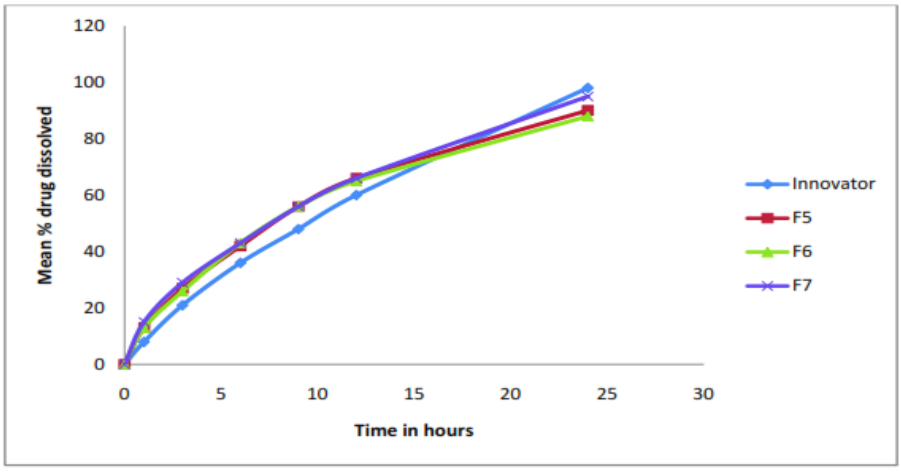
Comparative Dissolution Profile of All Formulations With Innovator



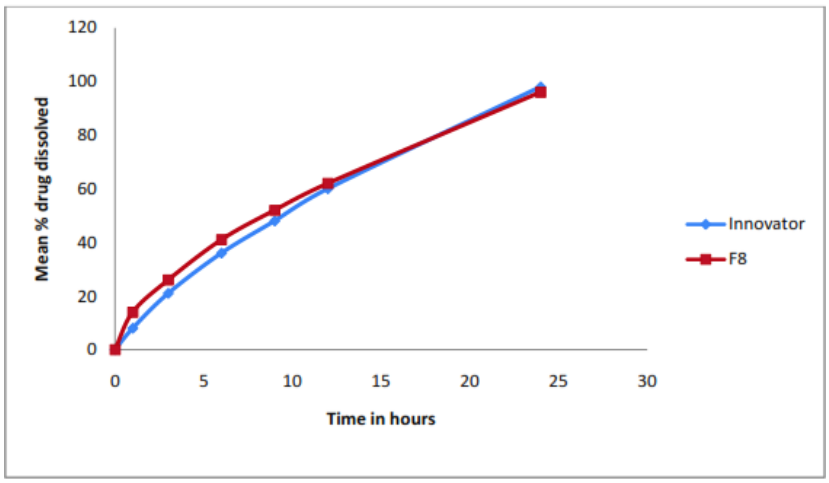
F1 and f2 formulation fig1



Innovator f3 and f4 formulations fig 2



Innovator f5 f6 and f7 formulations fig3



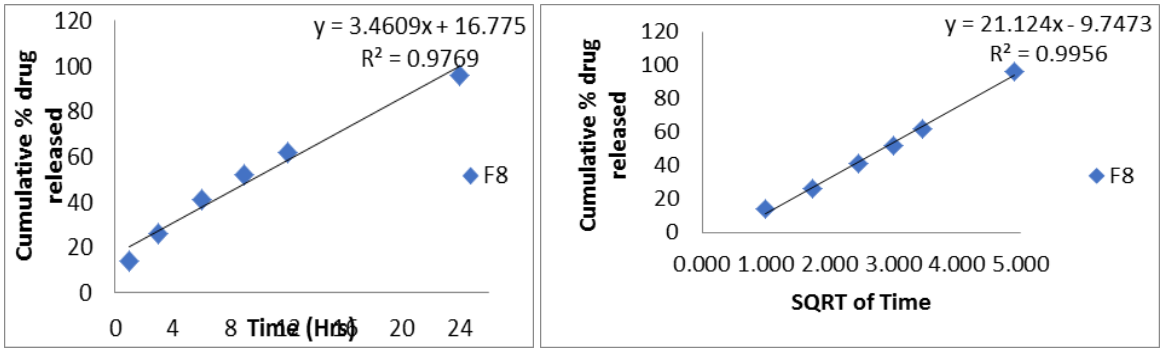
Innovator f8 formulations fig 4

Table 6

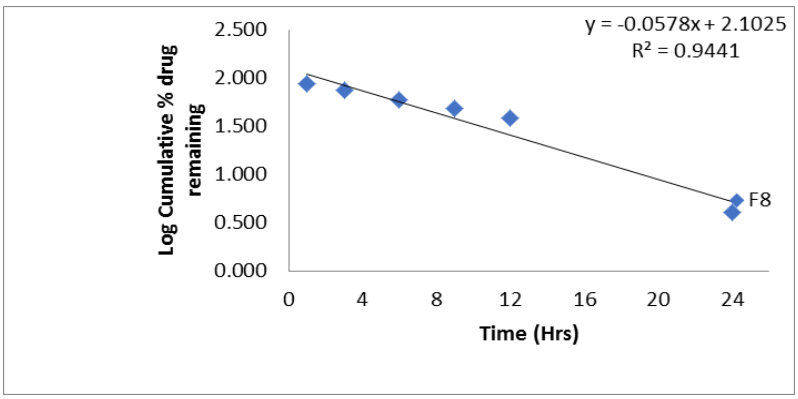
Mechanism of drug release	Regression (r^2)		Slope (n)	
	Reference	F8	Reference	F8
Zero order	0.982	0.976	3.811	3.460
First order	0.916	0.944	0.072	0.057
Higuchi	0.992	0.995	23.16	21.12
Korsmeyer peppas	0.997	0.999	0.787	0.607
Hixon crowell model	0.973	0.973	0.140	0.121

The release kinetics of the drug was observed to fit best with Korsmeyer Peppas having Regression coefficient of linear line as 0.999 and slope(n) was 0.65 i.e., n value was between 0.45 and 0.89 this indicates anomalous transport (Non Fickian diffusion).

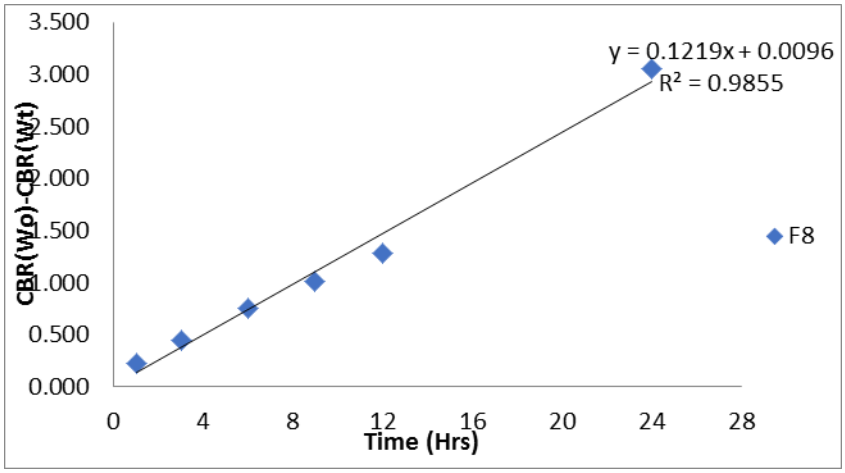
Pharmacokinetics



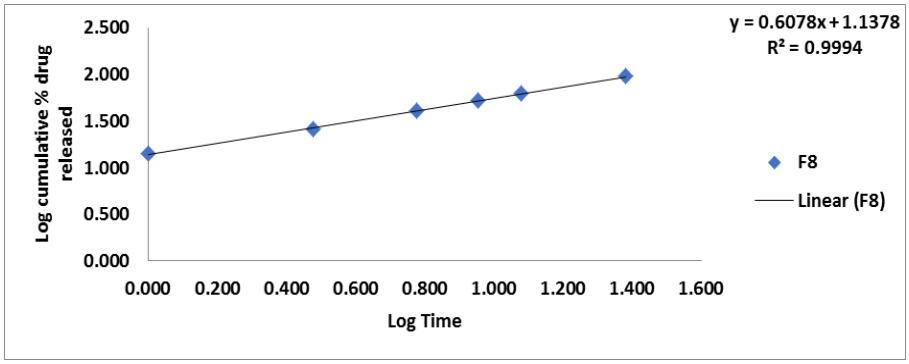
Zero order kinetics for F8 FORMULATION fig 5



FIRST ORDER KINETICS FOR F8 FORMULATION fig 6



HYGUCHI PLOT FOR F8 FORMULATION fig 7



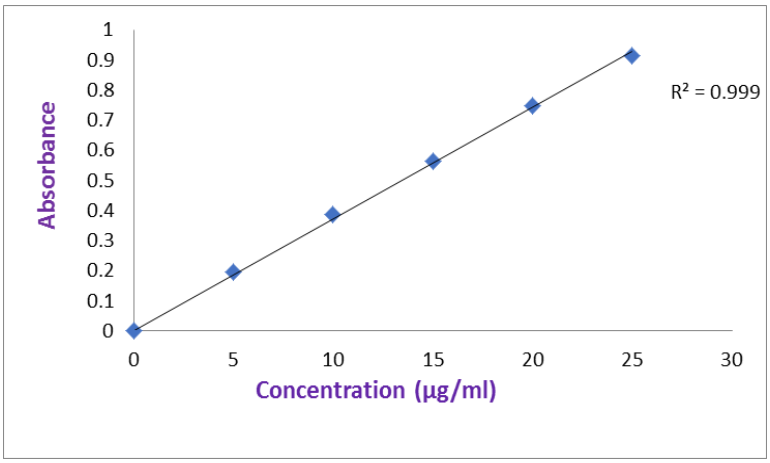
HIXON CROWWELL PLOT FOR FORMULATION F8 fig 8

RESULT AND DISSUSTIONS

DATA FOR CALIBRATION CURVE

Table 5

S. No.	Concentration(µg/ml)	Absorbance at 260nm (Avg ± s.d, n = 3)
1	0	0
2	5	0.197 ± 0.02
3	10	0.386 ± 0.06
4	15	0.563 ± 0.08
5	20	0.749 ± 0.04
6	25	0.902 ± 0.03



Calibration curve of Niacin.

KORSMEYERPEPPAS PLOT FOR FORMULATION F8 fig 9

CONCLUSION

Among all formulations, Formulation 8 containing NIACIN1000 mg per tablet was developed employing Methocel K 100 M, Cutina HR, Aerosil in dry mix is similar and equal to the innovator product in respect of all tablets properties and dissolution profile. No significane change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of 2 months at 40^{o} C and 75%RH. Hence the study resulted in the development of NIACIN prolonged Release Matrix tablets comparable to the innovator product for Niacin fulfilling the objective of the study. The identified formula shall be utilized for the formulation development and other studies for successful launching of the product as it was proved to be stable and robust, cost effective compared to osmotic device.

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