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Study on Influence of Fast Disintegrating Agents in In-Vitro Drug Release of Anti- Cancer Drug

*KARTHICK.M, R. MANIVANNAN, C. SRINIVASAN, J.SWARNAMBIGAI,D. VINOTHINI, Y. PRAKASHRAJ, SREEJITH SASIKUMAR,

[Department of Pharmaceutics, Excel College of Pharmacy, Komarapalayam, Namakkal, Tamilnadu, India]
Corresponding author:KARTHICK.M mail id: karthickm.m4@gmail.com ,8667468604

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ABSTRACT:
The current research focuses on Imatinib fast-acting tablets. Certain kinds of leukemia are treated with imatinib. The primary issue with the formulation of Imatinib is its long half-life, which causes a lag in peak plasma concentration. The notion of using super disintegrants to create fast dissolving tablets is a realistic way to achieve quicker disintegration and dissolve. Fast dissolving tablets were madeby direct compression technique which employeessuperdisntegrants such as crospovidone,sodium starch glycolate&croscarmellose sodium, among different approaches of manufacture.Free compaction criteria such asCarr's index,bulk density, angle of repose&tapped density, as well as post compression methods such as weight variation, friability, hardness, anddisintegration time, drug content uniformity, and In vitrodrug release study, were analyzed on the prepared Imatinib tablets. The F9 formulation of Imatinib indicates a maximum drug release of 30 minutes when compared to other fast dissolving tablets (100.3 %).

Key Words: Imatinib, Croscarmellose, Crospovidone, Sodium Starch Glycolate, Fast Disintegration, In vitrodissolution.

I. INTRODUCTION:

CANCER:

Cancer is a condition in which abnormal types of the body's cells multiply and spread uncontrollably. Oncology is the field of medicine that studies, diagnoses, treats, and prevents cancer. People of all ages, even fetuses, are susceptible to cancer, although the risk of most types rises about age 33. All malignancies begin in cells, the basic unit of life in the human body. Cells of several sorts make up the human body.The above nucleus divides and extend in a controlled process that produces new cells as necessary to keep the body flowing efficiently. As cells mature or get injured, they expire and are regenerated. This organizedprocedure, though, can occasionally go wrong. A cell's genetic material [DNA] can be damaged, resulting in mutations that interfere with normal cell development and division [1]. The annualized rate of new leukemia cases in men and women was 14.3 per 100,000. Men and women deceased at a rate of 6.1 per 100,000 each year. These statistics are based on cases from 2020 to 2021 and mortality from 2019 to 2021, and are age-adjusted. According to forecasts for 2019–2020, 1.6 % of male and female were diagnosed to be a terminal malignancy at certain point during respective lifetimes[2].

IMATINIB:

Imatinib is one of the first cancer treatments to show promise as a revolutionary cancer therapy method. Imatinib, a selective tyrosine kinase inhibitor (TKI), provides a therapeutic breakthrough as a targeted treatment for BCR-ABL, c-KIT, and PDGFRA. It has become the first-line treatment for a variety of malignancies.It has shown potential in treating of gastro-intestinal mesenchymal tumors, clonal basophilic diseases, Philadelphia chromosome positive acute lymphatic leukemias,steroid-refractory chronic graft versus host disease& steroid-refractory chronic graft versus host disease, in addition to CML, due to its anti-PDGFR activity. Imatinib's introduction has dramatically improved patient outcomes and sparked more study into the development of designer medicines with molecular targets[3].

The need for the quicker dissolving formulation grows with each passing day. As a result, the pharmacist must create Super disintegrants, for example, potent atmodest concentrations, have a disintegrating rate at higher values & are highly immediate setting potent [4]. Due to expanding pressure applied in the exterior or radial orientation, these super disintegrants cause

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the tablet to rupture or vast rise in the quantity of granules to stimulate disintegration [5].

The oral route has become one of the most effective approaches of drug delivery due to its simplicity of administration, patient acceptability, sterility limits, and adaptability of dosage form design. Conventional drug delivery techniques have been used to treat the majority of acute and chronic illness patients for decades. The most often prescribed medications are still those that use conventional drug administration mechanisms. Traditional oral medicine formulations are designed to deliver the active component suddenly after administration through oral route in order to ensure rapid and complete systemic pharmaceutical permeability.[6].

The process of unmodified drug transportation from the site of delivery to systemic circulation is referred to as drug absorption.

Noyes – Whitney equation, which proves the dissolution rate for even the components having poor soluble nature.

$$\frac{dc}{dt} = \frac{AD\,(C_S - C)}{h}$$

Where,

dc/dt = rate of dissolution

A = surface area available for dissolution

D = diffusion coefficient of the compound

C_s = solubility of the compound in the dissolution medium

C = concentration of drug in the medium at time t

h = thickness of the diffusion boundary layer adjacent to surface of the dissolving medium.

FAST DISINTEGRATING TABLETS:

The words "fast dissolving tablets" refer to the new technology of rapid-disintegrating dosage forms. The solid dosage form disintegrates&dissolves fast in the lingual route, culminating a dissolved state that doesn't require the use of liquid.To formulate fast disintegrating tablets containing Imatinib using a direct compression technique, which results in increased absorption by decreasing t max and solubility with different kinds of superdisintegrantslikesodium starch glycolate,croscarmellose sodium&crospovidone.It has a greater start of effect than traditional oral dose forms and hence improves patient adherence[7].The disintegration time of Imatinib tablets within different batches varied between 10-12 minutes, and their half-life is 14 to 18 minutes [8].

II. MATERIALS AND METHODS:

MATERIALS USED:

Imatinib - Arizest Pvt Ltd, Banglore.
Crospovidone - Ozone international, Mumbai.
Croscarmellose - Himedia laboratories, Mumbai.
PVP K 30 - Himedia laboratories, Mumbai.
Sodium starch glycolate - Himedia laboratories, Mumbai.
Magnesium sterate - Himedia laboratories, Mumbai.
Talc - Sd fine –chem limited, Mumbai.
Mannitol - Kemphasal pharmaceuticals.

Method of preparation of tablets by direct compression[9]:

The numerous tablets were made in an attempt to find the optimal tablet with the best solubility and bioavailability. The tablet formulations were listed in table 1.

Process:-

Step1:-All of the components were processed according to the criteria below:

Sift the active ingredient mixture (Imatinib) at mesh #40

Sift the direct compressible vehicles MCC at mesh #30

Sift the disintegrates (Crospovidone, Croscarellose sodium, Sodium starch glycolate)

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Sift the lubricants and glidants of (Magnesium stearate and talc)

Step2:-Preparation of blend

Ingredients was blended for 10 minutes after being put into a former polyethylene bag.

Step3:-Compression

12 stationary rotary punching machines were used to compact the imatinib mix until the necessary rigidity was achieved.

III. TABLET FORMULATIONS:

TABLET FORMULATIONS

S.NO	Ingredients (In mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Imatinib	400	400	400	400	400	400	400	400	400
2.	CP	5	7.5	10	---	---	---	---	---	---
3.	CCS	---	---		5	7.5	10	---	---	---
4.	SSG	---	---	---	---	---	---	5	7.5	10
5.	Magnesium Stearate	1	1	1	1	1	1	1	1	1
6.	Talc	70	70	70	70	70	70	70	70	70
7.	Mannitol	24	21.5	19	24	21.5	19	24	21.5	19

Table 1: Formulae for the preparation of tablets: (per tablet)

Characterization of granules[10]:

1. Angle of repose:

This method was calculated using thefreestanding cone& fixed funnel process. Gently pouring exactly weighted grains (5gm) into a funnel with a two-centimeter height (h) top till the conical heaps generated barely mentioned the funnel's apex.

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

Where, θ = angle of repose

h = height

r = radius

2. Bulk density:

The tapped bulk &loose density was calculated by using a small extent (20g) of granules from individual formulation that had been carefully shaken to break up any aggregates. Once the

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starting volume was measured, the cylinder was allowed to fill under its own weight onto a level surface at 2sec intervals from a height of 2.5 centimeter.

3. Hausner's ratio:

It measures the ratio of TBD to LBD and shows the flow characteristics of the powder.

Hausner's Ratio = =

TBD

LBD

4. Compressibility index (carr's index):

This method was constructed using the low bulk density and tapped bulk density to assess flow ability.

$$\text{Carr's index (\%)} = [\text{T BD} - \text{LBD}) \times 100)] /$$

5. Drug content uniformity:

Standard preparation: In a 50ml volumetric flask, a carefully weighed amount of pure Imatinib (5mg) is transferred.The absorbance was taken at 283 nm after being diluted and brought up to mark with 0.1 N HCl.

Sample preparation: In a 50 ml volumetric flask, a powdered tablet is inserted. To ensure the drug's entire solubility, the volume was then made up with 0.1N HCl and agitated for 25 minutes. After that, the answer went through a filtering process.A UV-Visible spectrophotometer was used to determine the absorbance of the sample solution at 283 nanometers.

Calculation:

$$A_t / A_s \times Sw/100 \times 100$$

A_t = Sample preparation absorbance
A_s = Standard preparation absorbance
S_w = working standard (mg) weight of imatinib.

Characterization of tablets[11]:

1. Hardness characterization:

Five pills were tested for hardness using a Monsanto hardness tester, and the mean and standard deviation were calculated.

2. Friability characterization:

For individual formulation, 6 tablets weight were taken. The pills were spin at twenty-five revolution per minute for four mins in a Roche friabilator. The pills were then cleaned and measured accurately.

$$F = (W_1.W_2/W_1)100$$

W_1 = initial weight of tablet
W_2= final weight of tablet

3. Disintegration characterization [12]:

Disintegration additives are added to the preparation to facilitate break up the tablet in to the minute granules & components particulate, enabling for rapid delivery of the dosage form from the solid matrix and, as a result, a larger surface area for further dissolution.Synthetic polymers ıs SSG, CP & CCS are the most often utilized lisintegrants.Because disintegration is a ;ity for dissolving in immediate-release ;, disintegration has a direct impact on the medication's therapeutic efficacy & it has to be tested& preferably amount, using specially developed test on disintegration.

4. Weight variation characterization:

This process was carried out as per the USP official percentage deviation of pills constraints,andeach formulation's tablets were evaluated using a digital balance.

$$\text{\% maximum positive deviation} = (W_H\text{-}A/A) \times 100$$

$$\text{\% minimum negative deviation} = (A\text{-}W_L/A) \times 100$$

Where,

W_H = Highest weight in mg
W_L = Lowest weight in mg
A = Average weight of tablet in mg.

5. Uniformity of Drug content:

Standard preparation: In a 50ml volumetric flask, a precisely weighed amount of pure Imatinib (5mg) is transferred. After being dissolved and brought up to volume with 0.1 N HCl, then at 283 nanometers the absorbance was determined.

Sample preparation: A tablet is pulverized and placed in a volumetric flask containing 50 ml of capacity. Then the volume is made up with 0.1N HCl and agitated for 25 minutes to verify that the medication was completely dissolved. The solution was then filtered. The sample solution absorbance wasrecorded at 285 nm in a UV-Visible spectrophotometer.

$$A_t/As \times S_w/100 \times 100/S_t \times A_v$$

A_t = Absorbance of sample preparation
A_s = Absorbance of Standard preparation
S_w = weight at Imatinib working standard (mg)
S_t = weight of Imatinib tablet (mg)
Av= Average weight of tablet (mg)

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6. In-Vitro Drug Release Studies (Dissolution studies)[13]:

Dissolution procedure:

Apparatus: USP-Type 2 (Paddle)

RPM: 50
Dissolution Medium: 900 ml
Medium: 0.1N HCl.
Temperature: $37^0 \pm 0.5^0$ C

Procedure:

The delivery of Imatinib from the formulations was examined for thirty minutes in 900 ml dissolution solvent (0.1N HCL) using a USP dissolving paddle assembly fifty revolution per minute at $37^o \pm 0.5^0$ C. After taking (1 ml) at various time intervals, filtered&diluted to ten milliliters with the dissolving fluid, the drug concentration was measured using a UV-visible spectrophotometer at 285 nm. To keep the dissolving volume constant, an equivalent volume of new dissolution media was substituted. The formula derived from a calibrationstandard curve; the cumulative percentage of drug delivery was computed.

7. In vitrorelease order kinetics of fast disintegration tablet Imatinib[14]:

1. Zero order kinetic model – Cumulative percent drug released versus time.
2. First order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

1. Zero order kinetics: -

$A_t = A_0 - K_0t$

The valuesfollow zero-order release kinetics with a slope of K0 if the plot is linear.

2. First orderkinetics: -

$$\text{Log } C = \log C_0 - K_t / 2.303$$

A straight line emerges when plotting log cumulative percent medication remaining vs time, demonstrating that the release is guided by first order kinetics You would get the constant 'K' by calculating 2.303 with slope values.

3. Higuchi's model: -

$$Q = [D\varepsilon / \tau (2 A - \varepsilon Cs) Cst]^{1/2}$$

When cumulative drug release is plotted against the square root of time, a straight line shows, demonstrating that the drug was released via diffusion. The slope, according to Higuchi, is equal to 'K'.

4. Korsmeyer equation / Peppa's model: -

$M_t / M_a = Kt^n$

The results were fitted to the well-known exponential equation (Korsmeyer equation / peppa's law equation) to describe drug release behaviour from polymeric systems, in order to examine the mechanism of drug release from Imatinib prolonged matrix tablets.

IV. RESULT AND DISSCUSSION:

Imatinib was utilized as a model medication for cancer therapy, and it is created using the direct compression method, which included varied quantities of fast disintegrating agents, talc as a diluent, and a lubricant for efficient pharmaceutical release, magnesium stearate is used.

In 9 formulations (F1-F9) the concentrations of rapid disintegrating agents (sodium starch glycolate,croscarmellose sodium,&crospovidone) were generated and examined for various physico-chemical features as well as in-vitro drug release studies in this work. Based on in-vitro release tests, the most effective formulation (F9) was chosen.

Preformulation Studies (Compatiblity Studies):

An FT-IR spectrophotometer was used to perform the compatibility tests. The infrared spectrum of pure Imatinib was analyzed to the infrared spectrum of an Imatinib physical combination (SSG, CP, and CCS). Any characteristic's peaks do not arise or disappear. This demonstrates that the medicine and the excipients do not interact chemically.

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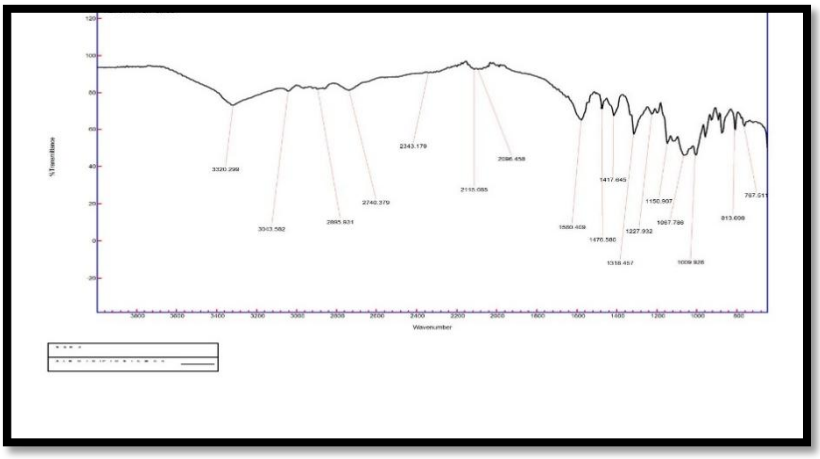

Fig-1: FTIR Spectra Imatinib and Croscarmellose sodium

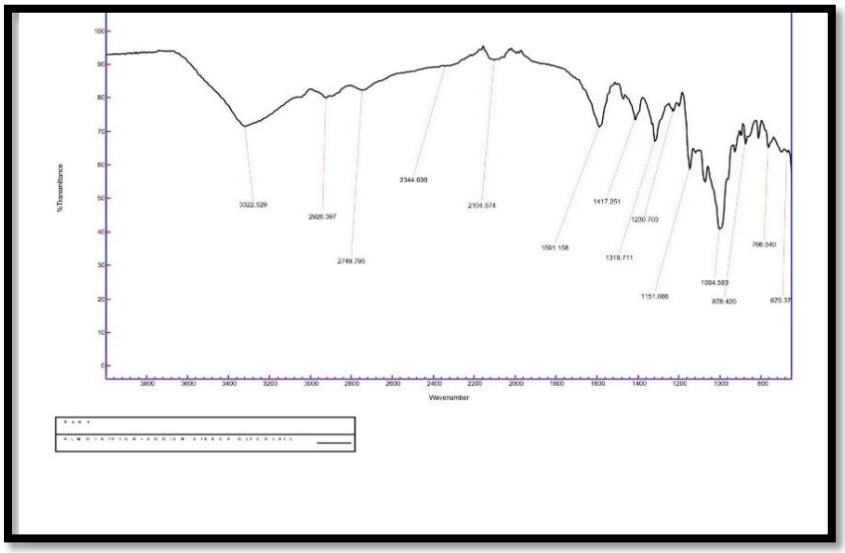

Fig-2: FTIR Spectra Imatinib and Sodium starch glycolate

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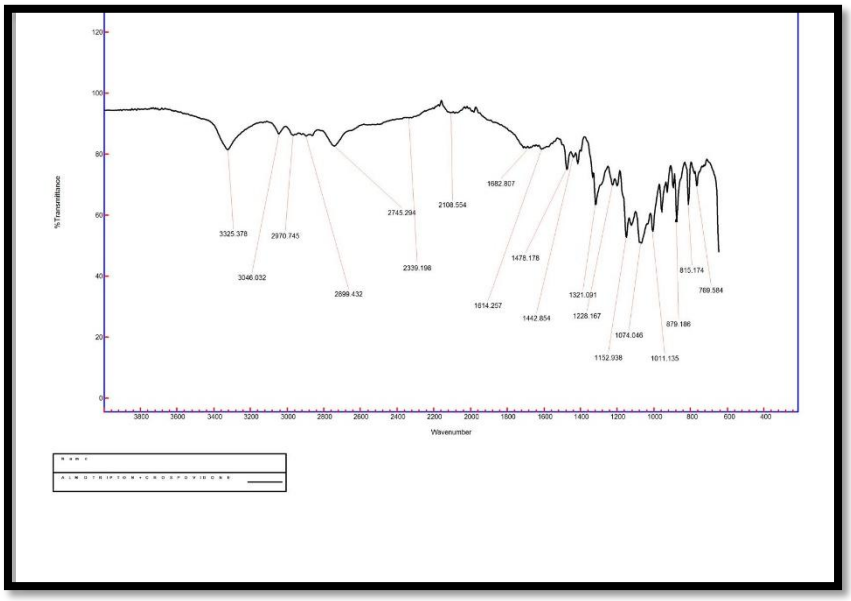

Fig-3: FTIR Spectra Imatinib and Crospovidone

Standard calibration curve of Imatinib:

The standard curve for Imatinib was determined using Beer's law, which was obtained by plotting absorbance (nm) versus concentration (mcg/ml) at 285 nm.

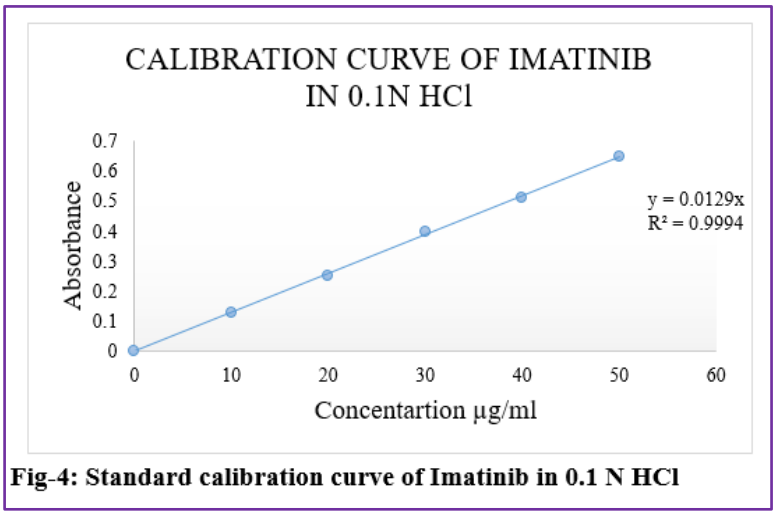

Fig-4: Standard calibration curve of Imatinib in 0.1 N HCl

Characterization of blending parameters of fast disintegrating tablets of Imatinib:

In blended granules of various formulations, angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, Hauser's ratio, and drug content homogeneity were all evaluated.

1. Angle of repose: Angles of repose varied from 28º00'' 1.1868 and 29º 65''±1.837. The findings were determined to be below 300, indicating that the mix had good flow properties.

2. Bulk density and tapped density: It is measured using bulk and tapped densities. The LBD and TBD, respectively, varied from 0.3969±0.004 to 0.4150 ±0.004 and 0.4652±0.007 to 0.4832±0.006.

3. Carr's index (compressibility index): The compressibility index (percentage) varied from 13.763±0.861 to 14.922±1.145.The mix was

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discovered to have free-flowing properties, with a result of less than 18 percent.

4. Hausner Ratio: The Hausner ratio varied between 1.160±0.011 and 1.176±0.016. The result suggests that the granules are free-flowing.

Physical characterization of oral fast disintegrating tablets of Imatinib:

The weight variation, hardness,friability, and drug content uniformity of imatinib fast dissolving tablets were examined, among other physical parameters.

1. Hardness test: All batches had a hardness of 4.5-6.5 Kg/cm2.

2. Friability test: The proportion of batches that were friable ranged from 0.047% to 0.094%.

3. Disintegration test: The sodium starch glycolate has disintegration (38 ±0.894 s to 143 ±1.276 s)

4. Weight variation test: The weight disparities in percent for all formulations. Within the Pharmacopoeias'5%-point limits, all of the formulations (F1-F9) passed the weight variation test

5. Uniformity of drug content: It was observed that drug concentration was constant across all formulations, ranging from 99.234±0.463 to 99.530±0.410.

In -vitro drug release for fast disintegrating tablets of Imatinib:

On a trial basis, the fast-disintegrating tablets were made and assessed. A total of nine formulations (F1-F9) were produced using sodium starch glycolate,croscarmellose sodium&crospovidone

Using a USP dissolving paddle assembly at 50 rpm and 37º ± 0.5º C in 900 ml of 0.1 N Hcl as the dissolution medium, the release of Imatinib from the fast-disintegrating tablet was examined.A UV-visible spectrophotometer set to 285 nm was used to determine the drug content. The dissolution tests lasted 30 minutes. The cumulative percentage of drug release was measured usinganformula developed from a standard calibration curve.

Formulations (F)	Absorbance (mm)	Concentration (mg/ml)	Amount of drug release (mg/900ml)	Cumulative %Drug release
F1	0.498	38.68	347.7	87
F2	0.552	42.79	385.1	96
F3	0.559	43.4	392	97
F4	0.534	41.3	373	94
F5	0.558	45.1	381	95
F6	0.559	43.4	392	97
F7	0.552	42.79	385.1	96
F8	0.570	44	392	99
F9	0.573	44.4	399	**100.3**

Table-2: *In vitro* Release profile for Imatinib fast disintegrating tablet formulation F1 to F9 at the time interval of 30 mins

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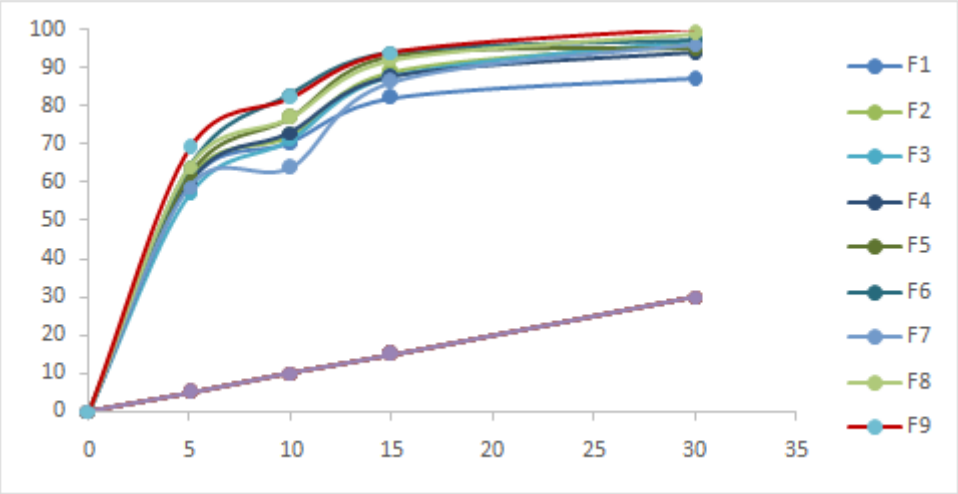

Fig-5: Percentage drug release profile for formulation F1 to F9

When all of these formulations of F1 to F9 are compared, the F9 formulation comes out on top, with a higher concentration of drug release of 100.3 percent at thirty minutes.

Formulation code	Zero order Plot(R^2)	First order Plot (R^2)	Higuchi Plot	Korsemeyer peppa's plot (R^2)	Possible mechanism of drug release
F1	0.771	0.8665	0.8512	0.8993	Fickian transport
F2	0.8219	0.96	0.9011	0.9422	Fickian transport
F3	0.8599	0.9869	0.9259	0.9604	Fickian transport
F4	0.8051	0.9323	0.888	0.9418	Fickian transport
F5	0.7051	0.8039	0.807	0.8828	Fickian transport
F6	0.6833	0.8844	0.7942	0.874	Fickian transport
F7	0.8514	0.9625	0.8902	0.8846	Fickian transport
F8	0.8237	0.9918	0.9024	0.9546	Fickian transport
F9	0.8158	0.8731	0.8999	0.9576	Fickian transport

Table-3: Kinetic values obtained from different plots of Formulation (F1– F9)

V. CONCLUSION:

When compared F1-F8, the outcome of formulation F9, which contains sodium starch glycolate (10 mg), demonstrates maximal and superior release at the end of 30 minutes. This might be attributed to sodium starch glycolate's faster swelling process, smaller particle size, and lower cost when compared to crospovidone,sodium starch glycolate, and croscarmellose sodium.as a result of this research, is a preferable super disintegrating agent in In vitro drug release and is also more cost efficient.

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