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DEVELOPMENT AND EVALUATION OF GLIPIZIDE MATRIX TABLET

***V Puri,[1] ARath,[2] J Chandi**

1,2 Department of Pharmacy, Jeypore College of Pharmacy

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***Corresponding Author**

Vamsi Puri*,

Brilliant Group of Technical Institution ,Hyderabad

ABSTRACT

Matrix tablet is one of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression or granulation of blends of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of retardant. The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description. The result of showed that the formulation F10 follow zero order and release mechanism of drug through polymeric membrane was observed anomalous transport (Non-fickian) diffusion, which is also confirmed by Higuchi plot.

Keywords: Higuchi Model, Biodegradation

Introduction

Oral route of drug administration is most appealing route for delivery of medicine of varied dosage forms. The tablets is one among the most most well-liked dosage kind as a result of of its easy administration, accuratedosing and stability as compared to oral liquid dosage forms and compared to capsules, tablets are additional temper evident.

Various forms of tablets

A) Oral tablets for uptake

These tablets are meant to be swallowed intact along with a comfortable amount of potable water. Exception is cuttable pill. Over ninetieth of the tablets manufactured these days are eaten orally. This shows that this class of formulation is that the most well liked worldwide and also the major attention of the researcher is towards this direction.

1. standard compressed tablets
2. Multiple compressed tablets

a. Compression coated tablet b. superimposed tablet

c. Inlay tablet

3. modified release tablet
4. delayed action tablet
5. Targeted tablet

a. Floating tablet

b. Colon targeting tablet

6. chewable tablet
7. Dispersible tablet

B) Tablets employed in the oral cavity

The tablets beneath this cluster are aimed unharness active pharmaceutical ingredient in oral cavity or to supplynative action during this region. The tablets beneath this class avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and provides fast onset of action. The tablets developed for this region are designed to fit in proper region of oral cavity.

1. Lozenges and troches
2. sublingual tablet
3. Buccal tablet
4. Dental cones

5. Mouth dissolved tablet

C) Tablets administered by alternative routes

These tablets are administered by alternative route apart from the oral cavity then the medication are avoided from passing through gastro intestinal tract. These tablets is also inserted into alternative body cavities or directly placed below the skin to be absorbed into circulation from the location of application.

1. vaginal tablet
2. Implants

D) Tablets- other forms

The tablets under this class are required to be dissolved 1st in water or alternative solvents before administration or application. This answer is also for uptake or parentral application or for topical use relying upon kind of medicinal drug used.

1. Effervescent tablet
2. Hypodermic tablet

Matrix Tablet,[16,17,18]

One of the smallest amount sophisticated approaches to the manufacture of sustained unharness indefinite quantity forms involves the direct compression or granulation of blends of drug, retardent material, and additives to create a tablet during which drug is embedded in an exceedingly matrix core of retardent.

Materials used as Retardants in Matrix tablet

There are 3 classed of fabric used as unharness retardants in matrix pill formulations.

a) **Insoluble inert polymers**

Tablets ready from these materials are designed to be ingested intact and not break an area in gi tract. eatentablets contain unreleased drug within the core. for instance polyethylene, poly vinyl chloride, ethyl cellulose, alkyl radical acrylate - methacrylate polymer.

b) **Insoluble, erodable polymers**

These kind matrices that management unharness through each pore diffusion and erosion. unharnesscharacteristics ar thus additional sensitive to biological process fluid composition than to the completely insoluble compound matrix. Total unharness of drug from wax-lipid matrices isn't potential , since a definite fraction of the dose is coated

with impermeable wax films. for instance carnuba wax together with stearic acid, stearyl alcohol, Castor wax and Triglycerides.

c) **Deliquescent Polymers**

This cluster represents non-digestible materials that kind gels in place. Drug release is controlled by penetration of water through a gel layer created by hydration of the polymer and diffusion of drug through the swollen, hydrousmatrix, additionally to erosion of the gelled layer. The extent to that diffusion or erosion controls release depends on the compound electoral for formulation similarly as on drug compound quantitative relation. for instancemethyl cellulose, hydroxyl radical ethyl cellulose, hydroxypropyl methylcellulose,Sodium alginate.

Types Of Matrix Tablet[19]

a)Hydrophilic Matrix tablet

For example sodium carboxymehylcellulose, methylcellulose, hydroxypropyl- methylcellulose, hydroxyethylcellulose, polythene chemical compound, poly vinyl pyrrolidine, poly vinyl acetate, gelatin, natural gums etc. severalindustrial proprietary hydrophilic matrix systems are presently in use, like synchron technology and hydrodynamically balanced system.

Main benefits of deliquescent matrix systems are easy manufacture and excellent uniformity of matrix tablet.

b)Fat Wax Matrix Tablet

The drug may be incorporated into fat wax granulations by spray congealing in air, mix congealing in AN liquid media with or with out the help of surfactants and spray drying techniques. for instance polythene, alkyl polysaccharide, chemical group esters of alter resins has been additional to switch the drug release pattern.

C) Plastic Matrix Tablets

For example polyvinyl chloride, polyethylene, polyvinyl acetate, vinyl chloride polymer, vinyllidine chloride, propenoate or alkyl radical methacrylate polymer, ethyl cellulose, cellulose ester, polystyrene.

With plastic material(s) tablets may be simply ready by direct compression of drug provided the plastic material may be comminuted or granulated to desired particle size to facilitate mixture with drug particles.

Method:

Present work was carried out to style and measure the sustained unharness tablets of the

candidate drug.

The study was planned to hold go in the subsequent stages.

Phase – I

Preformulation study of the Active powder drug. Preformulation study victimisation Ft- IR study.

Preparation of standard curve.

Phase – II

Formulation and analysis of sustained release matrix tablets.

Evaluation of matrix tabletsis done my the method that follows:

Physical analysis

Drug content

Uniformity of dosage units

Dissolution study

Drug release characteristics

Dissolution kinetic study

Dissolution profile of market available sustained release 10mg tablet. Investigation of drug release mechanism

Phase – III

Stability study of the selected formulations as per ICH guideline.

Evaluation of tablets

1. Uniformity of weight
2. Hardness
3. Friability
4. Drug content
5. Invitro dissolution study
6. Invivo studies

Flow Property Measurements

It is important parameter to be measured since it affects the mass of uniformity of the dose. it's typically fore told from flow property, Density, broached density softness index and Hausner quantitative relation.

Angle of repose:

Angle of Repose ;is found between surface of pile and horizontal plane horizontal plane. it's typically determined by fastened funnel technique and is that the live the flow ability of powder/granules.

Procedure

Weight amount of glypizide was felt a funnel unbroken at a height of a pair of cm for the bottom. The powder is passed until it forms heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by mistreatment the formula.

$\theta = \tan^{-1}(h/r)$ or $\theta = \tan^{-1}(\text{height} / \text{zero.5 Base})$

Where θ = aŶgle of repose

h = height of the heap of pile r = radius of base of pile

TABLE 1: Flow Properties and Corresponding Angle of Repose:

Flow properties	Angle of repose
Excellent	25-30
Good	31-35
Fair – aid	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very Very poor	>66

Density :(g/ml)

Granules density, true density. Bulk density might influence sponginess, pill porousness, flow property, dissolution and alternative properties, Higher compression load is needed just in case of dense and arduous granules thatsuccessively increase the pill disintegration and drug dissolution time.

Density is sometimes determined by pycnometer.

Bulk density: Procedure

Weighed amount of glipizide was transferred into a fifty millilitre mensuration cylinder while not tapping throughout transfer the volume occupied by granules was measured. Bulk density was measured by victimization formula.

Pi=m/Vo

Where,

m = mass of the mix

Vo = untapped Volume

Results square measure tabulated in table nineteen

Tapped Density

Procedure

Weighed amount of glipizide was taken into graduate, volume occupied by granules was noted down. Then cylinder was subjected to 500/750 and 1250 faucets in tapped density tester (Electro science laboratory USP II) in keeping with USP, the mix was subjected for five hundred faucets the sharp Volume variation was calculated by following formula.

Pt = m/vi

Where,

m = mass of the mix

Vi = broached volume

The result's tabulated in chapter

Compressibility index (Carr's Index)

Compressibility is that the ability of powder to decrease in volume under pressure. compressibility could be a livethat obtained from density determination.

Procedure

Weight amount of glipizide transferred to fifty millilitre graduate, volume occupied was noted down. Then cylinder was subjected to 500/750 and 1250 faucets in broached density tester (Electro science laboratory USP II) the distinction between 2 tabs ought to be but a pair of. the proportion of compressibility index is calculated by using formula.

$$CI=V0-Vi/V*100$$

Where,

Vo: Untapped density Vi: broached density

Results square measure tabulate in table19

Table:02 compressibility index

Compressibility index	Flow characters
< 10	Excellent
11-15	Good
16-20	F
21-25	Passable
26-31	Poor
32-37	Very poor
> 38	Very very

Hausner Ratio:

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 – 1.5, it was determined by the ratio of tapped density and bulk density.

$$\text{Hausner Ratio} = Vo / V_i$$

Where,

Vo = untapped density

V_i = tapped densit

Table:03 Hausner ratio

Flow characters	Hausner ratio
Excellent	1.0- 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very Very poor	>1.60

Evaluation Of Tablets

The formulated tablets were evaluated for the following the physicochemical parameters,

General appearance:

The tablets prepared were creamy white in color, oval shape. They were smooth, uniform and free from crack and chipping.

Thickness and Diameter:

Thickness mainly depends up on die filling, physical properties of material to be compressed under compressional force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye.

The thickness and diameter were measured by using vernier calipers. The thickness should not vary beyond ± 5% of standard value.

Uniformity of Weight:

20 tablets were weighed collectively and individually from the collective weight. Average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limit or not. The tablets meet the I.P test if not more than 2 tablets are outside the percentage limit and of no tablets differs by more than 2 times the percentage limit.

Every individual tablet in a batch is uniform in weight and weight variation of any within permissible limits (± 10% for tablets weighing 80 mg or less ± 7.5%) for tablets weighing between

80 mg and 250 mg ± 5% for tablets weighing 250 mg or more.

Table:4 Weight Variation Test

Average weight of Tablets (mg)	Max. Percentage deviation (%)
130 or less	10
130 – 324	7.5
324 or more	5

Hardness:

Hardness of the tablet was determined using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet and zero reading was taken. The plunger was then forced against a spring by turning a threaded blot until the tablet fractures. As the spring was compressed a pointer ride along a gauge in the barrel to indicate the force.

The hardness of about 5kg is considered minimum for uncoated tablets for mechanical stability. The hardness is measured in terms of load/pressure required to crush it.

Friability test:

The roche friability test apparatus consists of circular plastic chambers divided in two compartments the chamber was rotated at a speed of 25rpm and these tablets were dropped by a 15 cm distance pre-weighed tablets were placed in the apparatus which was given 100 revolution after which tablets were weighed once again. The difference in two weights represents friability. The weight loss should not be more than 1%.

Where,

F = Friability,

W = Final weight,

Wo = Initial weight.

Percentage friability = [(intial.wt-final.wt)/ (intial.wt)] x 100

Drug content:

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 15mg of glipizide, dissolves in 30 ml of methanol with gentle heating on a water bath, cool and add sufficient methanol to produce a 50 ml. filter and dilute 5 ml of the filtrate to 50ml of methanol. Measure the absorbance of the resulting solution at 274 nm.

$$\frac{\text{Sample abs}}{\text{Standard abs}} \times \frac{\text{standard dilution}}{\text{sample dilution}} \times \text{weight to be taken}$$

In vitro dissolution studies

REF---Silverstein RM, Webster FX. Spectrometric identification of organic compounds, 6th edition. New York: John Willey& sons, Inc.; 1998

Acid stage:

750ml of 0.1N hydrochloric acid was placed in the vessel and the USP standard dissolution apparatus (II basket method) was assembled. The medium was allowed to equilibrate to temperature of 37±0.5^{O}C. One tablet was placed in the apparatus and the vessel was covered. The apparatus was operated for 2 hours at 50 rpm. The medium is

replaced with 0.1N hydrochloric acid and analyzed spectrometrically at 274nm with using SHIMADZU U.V.Visible spectrophotometer.

Buffer stage:

With the apparatus operation at 50rpm, to the fluid in the vessel 250ml of 0.2M tri-basic sodium phosphate that was equilibrated to $37^0C \pm 0.5^0C$ was added. Samples (5ml) were withdrawn at predetermined time intervals. The addition of 250ml of 0.2 tri-basic sodium phosphate to 0.1N hydrochloric acid converts into 6.8 pH buffer and analyzed spectometrically at 274nm using

Table 05 Dissolution studies in pH 6.8 phosphate buffer

Dissolution apparatus	**USP dissolution apparatus-2 (paddle type)**
Dissolution medium	0.1 N hydrochloric acid
Volume of receptor fluid	750 ml
Temperature	37±0.5
R	50
Total dissolution time	2hrs
Sampling time	30,60,90 and 120 mins
Sampling volume	5ml
Analysis	Specrophotometricaly at 274nm.

Table 06 Dissolution studies in 0.1N HCL

Dissolution apparatus	USP dissolution apparatus-2 (paddle type)
Dissolution medium	pH 6.8 phosphate buffer
Volume of receptor fluid	150 ml
Temperature	37±0.5
Rpm	50
Total dissolution time	10 hrs
Sampling time	3,4,5,6,7, and upto 12 hrs
Sampling volume	5ml
Analysis	Specrophotometricaly at 274nm.

The results of drug dissolution from maximum percentage to the minimum percentage are presented in a table. Comparisons of dissolution profile all the formulations are presented graphically .Mass degree of Swelling/eroding.

The mechanism of drug release from hydrophilic polymeric matrices involves solvent penetration, hydration and swelling of the polymer, diffusion of the dissolved drug in the matrix and erosion of the gel layer. Initially, the diffusion coefficient of drug in the dehydrated polymer matrix is low; it increases significantly as the polymer matrix imbibes more and more water and forms a gel, as time progresses. The hydration rate of the polymer matrix and thereby the gel formation and subsequent erosion depends significantly on polymer proportion, viscosity and to a lesser degree on polymer particle size.

Swelling and erosion studies were performed according to the method reported by Al-Taani and Tashtush, to understand the influence of swelling and erosion behavior on drug release and also to determine the effect of polymer viscosity on swelling and erosion. Matrix tablets were introduced into the dissolution apparatus under the standard set of conditions as specified for release rate studies. The tablets were removed using a small basket, and the swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were dried in a vacuum oven at 45^0C to a constant weight. Swelling (%) and erosion (%) were calculated according to the following formulas:

% swelling = S/R X 100 % Erosion = (T-R)/T X 100

Where,

S-Weight of the matrix after swelling

R-Weight of the eroded matrix

T-Initial weight of the matrix

Evaluation Of Release Characteristics

The release of the active ingredient from the preparation in the gastrointestinal tract is affected by many physiological factors including the mechanical force exerted by the digestive tract in relation to its movement and the volume, composition pH, surface tension and viscosity of the gastrointestinal fluid. Therefore, the in vitro release behaviors should be investigated under as many conditions as possible to understand effects of gastrointestinal variables on in vivo release. To achieve stable blood concentrations, it is generally desirable to prepare prolonged release dosage forms whose release rates are mainly pH, such as 1.2, and 6.8 representing typical gastrointestinal pH variation. Considering the variation in gastrointestinal motility, agitation rates should also any more than 2 levels among 50, 100, and 200 rpm, when the paddle method is used, at an appropriate pH. It is also desirable to perform release tests using different kind of apparatus.

Estimation Of Sustained Release Matrix Tablet Effect Of Hardness On Dissolution Rate

The tablet hardness having an impact on release curve and the total release time, increasing the hardness generally cause slowing of dissolution at a constant drug level because increase in binding agent (excipient level). Present study was carried on two different hardness of tablet same concentration of drug (10mg of ACTIVE).

Effect Of Intensity Of Agitation On *In Vitro* Release Rate

The tablets of optimized batch were studied to observe the effect of agitation on dissolution which was being carried out at 30, 50 and 100 rpm. The dissolution was carried out in pH 6.8 phosphate buffer with 0.1 N HCl.

***In Vivo* Studies Data Experimental procedure**

Anti diabetic activity

Study in normal rats: A group of ten albino rats weighing between 250-300 g were administered with 2 mg/kg weight Glipizide orally, for two consecutive days. Blood samples withdrawn from retro orbital puncture at 0,1,2,4,6 and 12 hours intervals. Blood samples were analysed for blood glucose levels by GOD/POD method using commercial glucose kits for serum Glipizide concentration by HPLC method.

Study in diabetic rats: diabetes was induced by the administration of alloxan monohydrate in the two doses i.e 100 mg and 50 mg/kg body weight, intraperitoneally for two consecutive days. A group of 10 rats with blood glucose levels above 250 mg/dL was selected for the study. The similar to the one conducted in normal rats was repeated in diabetic group.

Kinetics Of Drug Release

To study the study kinetics, data obtained from in vitro release were plotted in various kinetic models.

Zero order equation

The graph was plotted as % drug released Vs time in hours.

$$C=K_0t$$

Where,

K_0 – Zero order constant in concentration/time

t – Time in hours

The graph would yield a straight line with a slope equal to K_0 and intercept the origin of the axis. The results were tabulated and graph was shown.

First order equation

The graph was plotted as log % cumulative drug remaining Vs Time in hours.

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

Where,

C_0 - initial concentration of drug.

K- First order constant.

t- Time.

Higuchi kinetics

The graph was plotted as % Cumulative drug released Vs square root of time

$$Q = Kt^{1/2}$$

Where,

K – constant reflecting design variable system.

t - time in hours

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release. The results were tabulated.

Hixson and crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and crowell rate equation. The graph was plotted by cube root of % drug remaining Vs time in hours.

$$Q_0^{1/3} - Qt^{1/3} = K_{HC} X t$$

Where,

Qt – Amount of drug released in time t.

Q_0 - Initial amount of drug.

K_{HC} – Rate constant for Hixon crowell equation.

Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs time

$$M_t / M\alpha = Kt^n$$

$$\text{Log } M_t / M\,\alpha = \log K + n \log t$$

Where,

$M_t / M\alpha$ - fraction of drug released at time t

– Release time

K – Kinetic constant (incorporating structural and geometric characteristics of preparation)

n - Diffusional exponent indicative of the mechanism drug release.

If n value is 0.5 or less, the release mechanism follows Fickian diffusion and higher values of $0.5 < n < 1$ for mass transfer follow a non- fickian model (anamalous transport).

The drug release follows zero-order drug release and case – II transport if the value is 1. For the values of n higher than 1, the mechanism of drug release is regard as super case II transport. This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time. The results were tabulated.

- Zero Order Reaction - % Cumulative drug release Vs Time in hrs
- Korsmeyer – Peppas equation - log cumulative % of drug released Vs log time
  Higuchi kinetics - % Cumulative drug release Vs square root of time
- First Order Reaction – Log % Cumulative drug remaining Vs Time in hours
- Hixon and crowell erosion equation- cube root of % drug remaining Vs time in hours

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications.

Stability studies were conducted for the formulation F10 (Optimized batch). The reason for selection is, formulation have shown good results in *in-vitro* drug release studies. The stability study was performed as per following.

Preliminary Stability of the Optimized Batch:

The Optimized batches were charged on accelerated stability as per ICH guidelines.

Stability protocol of Sustained release tablet: Batch no: Optimized Batch (F10)

Pack: Blister

Table - 07 Storage condition

S.NO.	STUDY	STORAGE CONDITION
1	Long term	25°C±2°C/60%RH±5%RH
2	Intermediate	30°C±2°C/60%RH±5%RH
3	Accelerated	40°C±2°C/75%RH±5%RH

Testing Parameters:

The tablets were analyzed for hardness, friability and uniformity of drug content, after a period of 90 days..The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. And to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions.

Stability Studies Of Glipizide Sustained Release Tablets

The storage conditions used for stability studies were Accelerated condition (40°C±2°C/75%±5%RH) and Room Temperature (30°C±2°C/65%±5%RH). Samples of tablets were analyzed at 0 day, 15thday, 45 day and 60 day for physical characters and assay and were performed followed by in vitro dissolution test.

Test Performed

1. Assay
2. *In vitro* Dissolution Study
3. Test for other physical parameters (hardness, weight variation, friability).

Comparison of Dissolution Profile Between Optimized Formulation And Marketed Product

It was done as per procedure given as per *in vitro* release in this section. Graph of cumulative percentage drug release Vs time (hour) for both the optimized formulation and marketed product was plotted.

Result and Discussion

Glipizide raw material passed all the tests for identification. Percentage purity of raw material was determined to be %w/w. the correlation of coefficient for calibration curve in0.1N HCL was found to be 0.999. The linear regression analysis equation was found to be y =0.0158(X) +0.0023

The drug polymer interaction was studied by comparing the FTIR spectrum of the formulations FA1, FA2, FA3 to FA16 with that of Glipizide RS. The IR spectrum of formulation FA1, FA2, FA3 to FA16 shows the same characteristics frequency as that of Glipizide RS. And comparison shows that there is no drug interaction between the drug and other ingredients of formulation including excipients and such as lactose, starch, talc etc. Results of evaluation of granules are as follows,

- Angle of repose was found to be 30^0 It is considered as a free flowing material.
- Tapped Bulk density was found to 0.456 to 0.498 gm/ml.
- Carr's index was found to be of ϱ% to ϭϱ%.
- Hausners ratio was found to be 1.12 to 1.16. Within the specific limit of 1.00 to 1.50. The entire blend showed a good flow property.The bulk density, tapped density, compressibilty carr's index and Hausner's ratio were observe as it reveals that all the formulation blend having good flow characteristics and flow rate than raw material.

Loss on drying

Loss on drying was determined as per procedure given in material and methodology section. The results are illustrated in following tables.

Table-08 Observation for Loss on drying

Test	Specification	Observation
Granules ready for	Not more than 0.5%	0.39%

Physical compatibility test

Physical compatibility test was determined as per procedure given in material and methodology section.

Table 09 Physical Compatibility Test

Drug excipients blend	6 weeks		
	Control	40°C	40°C/75%RH
Candidate Drug	NC	NC	NC
Sodium alginate	NC	NC	NC
Carbopol	NC	NC	NC
Chitosan	NC	NC	NC
Xanthan gum	NC	NC	NC
Starch	NC	NC	NC
Colloidal silicon	NC	NC	NC
Magnesium stearate	NC	NC	NC

NC – No Change

Test	Observation	Inference
Description (colour change)	No changed of colour	Complies with the condition

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

Further to this all the formulated tablets designed as FA_1, FA_2, FA , FA_3, FA_4, FA_5, FA_6, FA_7, FA_8, FA_9, FA_{10}, FA_{11}, FA_{12}, FA_{13}, FA_{14}, FA_{15}, FA_{16}, were evaluated for its following physicochemical characteristics.

Thickness ranged from 5.01 to 5.42 mm. Thickness marketed formulation was found to be 5.18 mm respectively.

Uniformity of weight was observed to be within the limits. The maximum percentage deviation allowed is ± 7.5% for tablets of 200 mg (as per USP). All the tablet batches comply with the official test.

Hardness was observed to be 4.1 and 4.8 kg/cm^2. For marketed formulation the hardness was found to be 5.1 kg/cm^2. The hardness of about 4-5 kg/cm^2 is minimum for uncoated tablets for mechanical stability. All the formulations were found to have satisfactory hardness.

Friability of the formulations was observed between 0.221% to 0.721% w/w. friability of marketed formulation was found to be 0.286 % w/w respectively. Percentage of friability not more than 1% w/w is recommended limit. All the tablet batches were found to be within this limit.

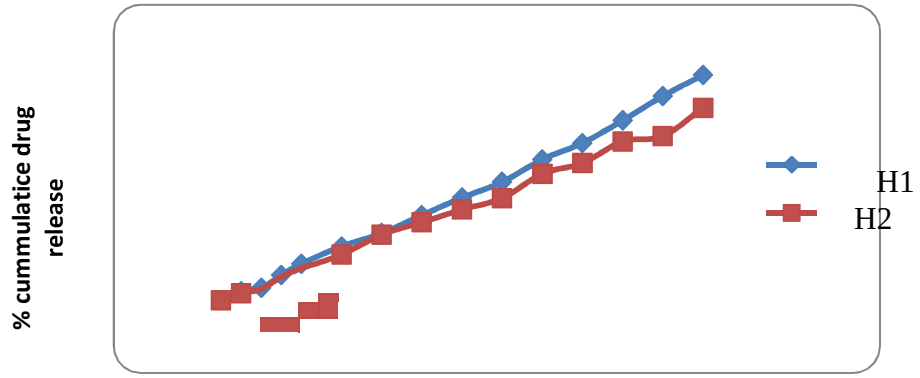
Estimation of Sustained Release Matrix Tablet

Effect of Hardness On Dissolution Rate For Formulation F10

Table – 10 Effect of hardness on dissolution rate

Time in hr	cumulative drug release for different Hardness	*Average of three
0	0.0	0
0.5	4.02	3
1	5.56	5
1.5	11.1	1
2	16.1	1
3	23.7	2
4	29.5	2
5	37.4	3
6	45.1	3
7	52.0	4
8	61.9	5
9	69.1	6
10	79.0	6
11	89.7	7
12	98.9	8

Fig No 01 Cumulative Drug Release Study



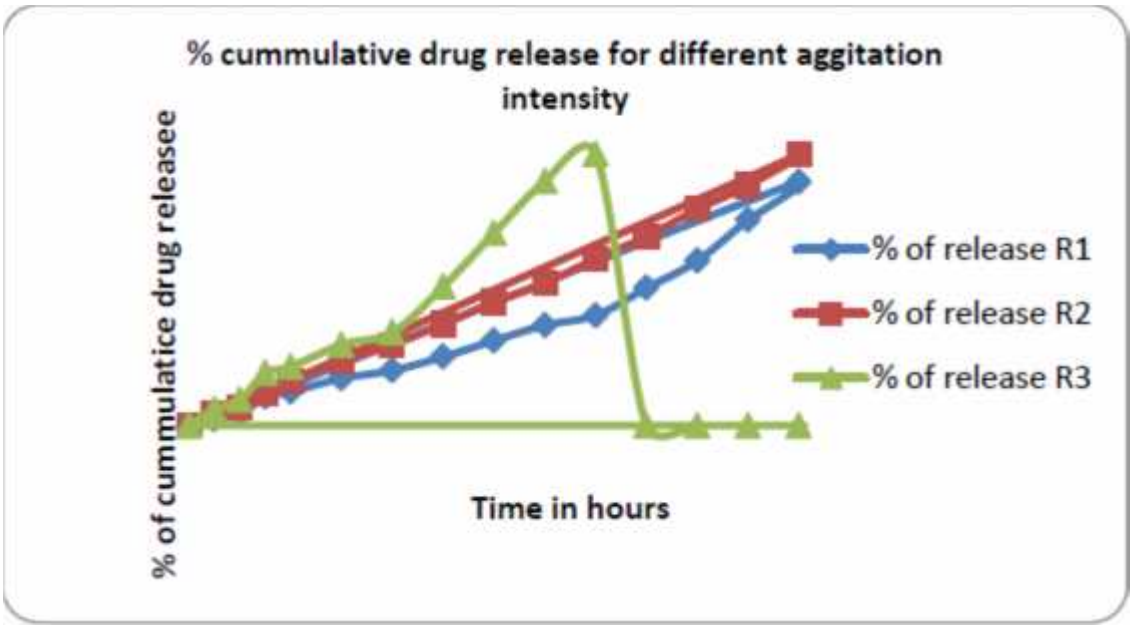
From the above data, revealed that the rate of drug release in case of hardness 1-5 kg/cm^2 is slow in comparison to that of hardness 1 – 7 kg^2.

Effect Of Agitation Intensity On *In Vitro* Release Rate For Formulation F10

Table-11 Effect of agitation intensity on Dissolution rate

Time (in hour)	Cumulative percent Drug Release		
	30 rpm*	50 rpm*	100 rpm*
0	0.0	0.0	0.0
0.5	2.25	4.02	5.95
1	4.23	6.56	9.53
1.5	10.59	11.60	19.25
2	12.36	16.10	21.53
3	17.25	23.74	29.58
4	20.15	29.58	34.12
5	25.12	37.03	50.83
6	31.06	45.10	70.31
7	36.67	52.03	89.27
8	40.29	61.03	99.25
9	50.26	69.02	-
10	60.24	79.09	-
11	75.24	87.78	-
12	89.10	98.93	-

Fig No 02 Cumulative Drug Release at different Intensities



Invitro Studies

Kinetic Study of Formulated Tablets

Investigation of the order and mechanism of drug release by plotting the in vitro data of optimized formulation F10 for zero and first order, higuchi and Korsmayer peppas equation were the observed slop values and regression co-efficient are given in table>>>. The result of table showed that the formulation F10 follow zero order and release mechanism of drug through polymeric membrane was observed anomalous transport (Non-fickian) diffusion, which is also confirmed by higuchi plot.

Determination Of Swelling And Eroding Behavior

The percentage sweeling and percentage erosion of the matrix tablets was totally dependent on the viscosity of the polymer used. The percentage sweelling increased with increase in polymer viscosity, while the percentage erosion decreased with increase in polymer viscosity. This was because higher viscosity grades of HPMC have higher and faster water absorption capacities and tend to swell more rapidly compared with the lower viscosity grades.

Stabilty Studies (As Per ICH Guidelines)

The fabricated extended release formulation (finally selected F10) was subjected to stability studies at 30°C±2°C / 65% RH±5% and 40°C±2°C / 75% RH±5% for 45 days. The product was evaluated for appearance and hardness every 15days. Drug polymer compatibility, drug content and drug release studies were conducted as per the planned scheduled as above.

1. Storage condition at 30°C±2°C/ 65% RH±5%

a) Description

Table-12 Test of various physical parameters

Test	Inference
Hardness	Complies with the stability condition
Weight variation	
Thickness	
Friability	

b) Dissolution data of percent cumulative drug release for formulation F10

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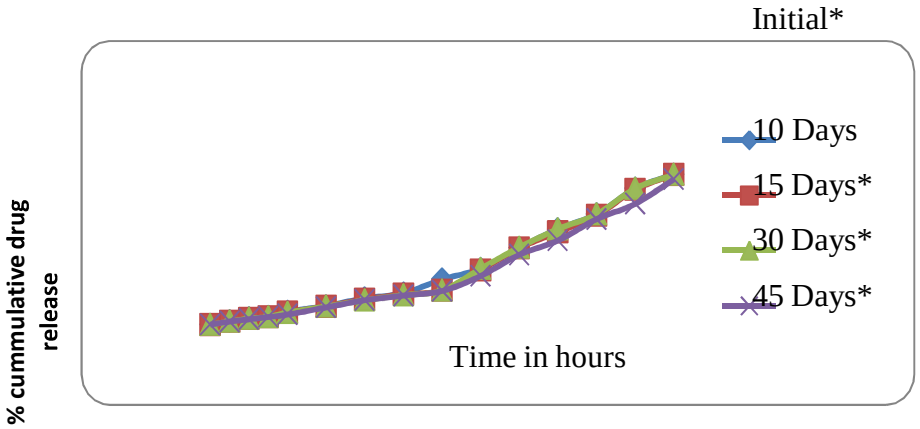
Table 13:Comparison of dissolution data of stability sample at room temperature

Time (in	Initial*	15 Days*	30 Days*	45 Days*
0	0.0	0.0	0.0	0.0
0.5	2.25	2.12	2.01	1.98
1	4.25	4.01	3.95	3.51
1.5	5.25	5.12	5.01	4.95
2	8.53	8.01	7.95	6.58
3	12.25	12.01	11.89	11.25
4	17.25	16.59	16.01	15.95
5	20.65	19.80	19.28	19.01
6	29.59	22.51	22.40	22.01
7	36.67	35.68	36.67	31.86
8	50.29	50.12	50.58	45.80
9	62.64	60.60	62.62	55.06
10	72.25	71.37	72.25	69.02
11	89.10	88.38	89.10	79.01
12	98.36	98.19	98.15	95.10

Fig No 03 % cummulative drug release at room temperature



2. Storage condition at 40°C± 2°C / 75% RH± 5%

Table 14 Storage description

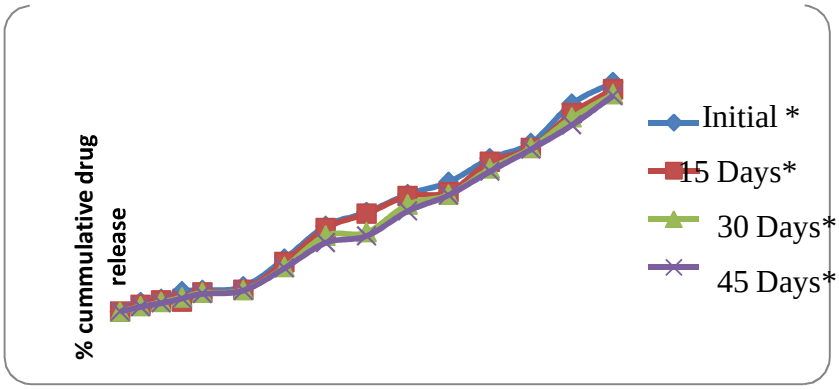
Test	Inference
Hardness	Complies with the stability condition
Weight variation	
Thickness	
Friability	

b) Dissolution data of percent cumulative drug release for optimized formulation F10

Table 15 Comparison of dissolution data of stability sample at Accelerated temperature

Time in hour	Initial *	15 Days*	30 Days*	45 Days*
0	0	0	0	0
0.5	3.93	2.89	2.12	2.02
1	5.26	4.56	4.01	3.59
1.5	8.56	4.25	5.98	5.58
2	9.18	8.25	8.01	7.59
3	10.65	9.24	9.15	9.01
4	22.59	21.12	19.02	18.59
5	36.67	35.74	32.54	29.48
6	42.53	41.98	33.96	32.42
7	50.29	49.58	45.90	43.06
8	55.59	51.25	50.12	49.98
9	65.64	64.25	61.25	60.12
10	72.25	70.15	70.12	69.58
11	89.10	85.19	83.15	80.01
12	98.36	95.29	93.25	92.56

Fig.04 Percentage Cumulative Drug Release at Accelerated Temperature



Time in hours

Comparison of Dissolution Profile Between Optimised Formulation And Marketed Product

The comparison of dissolution profile between optimized formulation F10 and marketed product was done as per procedure given as per *in vitro* release in material and methodology section. Graph of cumulative percentage drug release Vs time (hour) for both the optimized formulation F10 and Marketed product was plotted

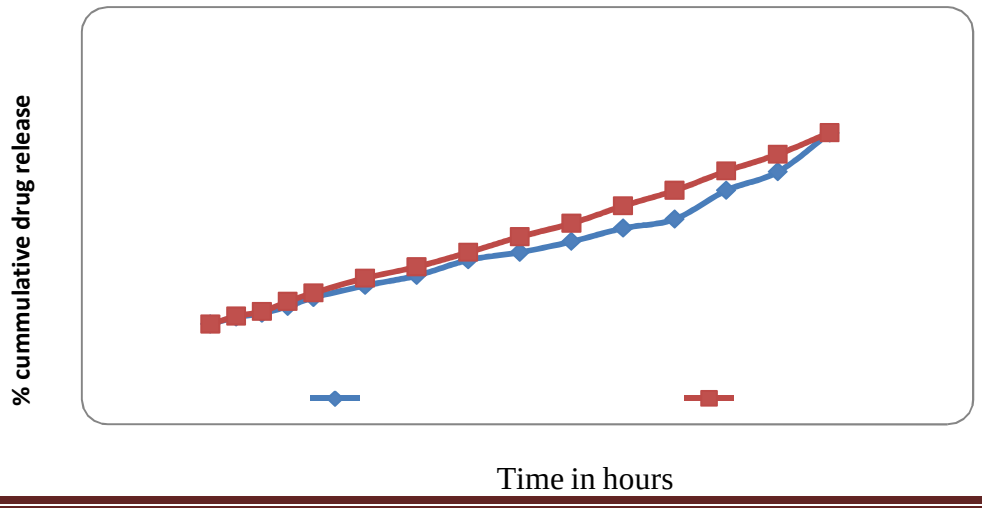
***IN VITRO* RELEASE STUDY OF MARKETED FORMULATION AND F10**

Table 16: *In vitro* release comparison of marketed formulation and F10

Percent cumulative drug release for marketed product		
Time in	Marketed formulation	F10 formulation
0	3.52	4.02
1	5.56	6.56
1	9.12	11.60
2	13.71	16.10
3	19.84	23.74
4	25.02	29.58
5	33.07	37.03
6	37.05	45.10
7	42.64	52.03
8	49.52	61.03
9	54.22	69.02
1	69.08	79.09
1	78.64	87.78
1	98.70	98.93

*Average of three determinations

Fig 04 : Invitro release comparison of marketed formulation and F10



Conclusion:

Matrix tablets enhances drug activity for a prolonged period of time..It enhances bioavailability. It has a greater scope in future. Frequent dosing is avoided

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