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FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF ECONAZOLE

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Abstract: - Granules made with the wet granulation process were compressible formed into sustained-release tablets for the efficient formulation of econazole. Together with excipients including talc, magnesium stearate, microcrystalline cellulose, PVP K30, guar gum, and pectin were used as binding agents. Econazole's solubility profile revealed that it was limitedly soluble in water, moderately soluble in chloroform, and highly soluble in benzene, methanol, and acetone. A range of in vitro assessments were performed on the produced tablets, including hardness, friability, weight variation, disintegration time, drug content, and dissolving behaviour tests. The release kinetics were first-order, with an R2 value of 0.983 and an equation of y = -0.077x + 2.182. Every formulation showed acceptable drug release and dissolution patterns in vitro. This study indicates that the addition of guar gum effectively adjusted the release rate, suggesting that it is a feasible technique for the creation of sustained-release matrix tablets, even if a hydrophilic matrix alone was not adequate to control the release of econazole over 24 hours.

Keywords: - Econazole, Sustained-release tablets, Wet granulation, Release kinetics, Guar gum

Introduction

Oral drug delivery has been recognized as the most extensively used route of administration among all the methods that have been used for systemic drug delivery via various pharmaceutical products in various dose forms. The oral route's success can be ascribed in part to its ease of administration. The short stomach residence times (GRTs) hamper the oral continuous medication administration strategy. Rapid GI transit can limit complete medication release in the absorption zone, lowering the supplied dose's efficacy.[1]

Additionally, orally delivered medications can be targeted to specific sections of the GI tract for localized therapy of pathological illnesses such as stomach and colorectal malignancies, infections, inflammations, bowel diseases, gastro-duodenal ulcers, and gastroesophageal reflux.[2]

Tablets are the most accepted drug delivery systems for oral administration. They are convenient to manufacture on a large scale with reproducibility, and stability and have high patient acceptability. The major drawback of conventional tablets is need of frequent administration to maintain a therapeutically effective concentration of drug in the blood.1 Conventional oral drug products, such as tablets and capsules release the active drug for oral administration to obtain rapid and complete systemic drug absorption. However, fluctuations in plasma concentration below MEC lead to a loss of therapeutic activity.[3]

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period after administration of a single dose. The main aim of preparing sustained-release formulations was to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed, and providing uniform drug delivery. [4] Ideally, two main objectives exist for these systems: Spatial delivery, which is related to the control over the location of drug release. Temporal drug delivery the drug is delivered over an extended period during treatment (SR) and an idealized zero-order controlled release (ZOCR) drug delivery system.[5]

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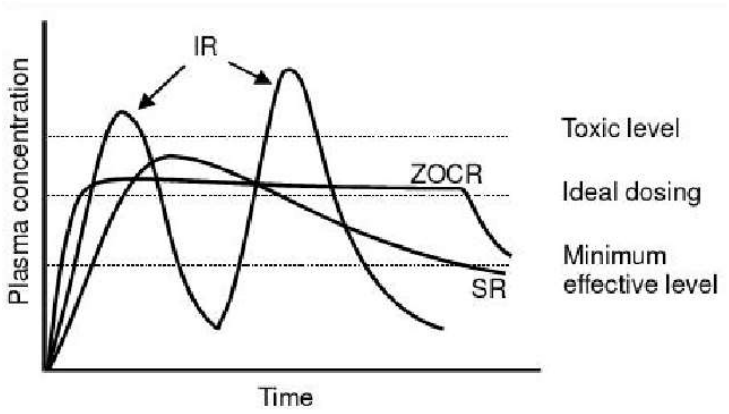

Figure 1: Graphical representation of plasma concentrations of a conventional Immediate Release (IR), a Sustained Release

Manufacturers have used a variety of terminology (and abbreviations) to characterize product kinds and features over the years, including sustained release (SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended-release (ER), timed release (TR), and long-acting (LA).[6]

Sustained release: -It is significantly influenced by the external surroundings into which it will be discharged.

Controlled release: - Controlled release (CR) systems deliver drug release in amounts sufficient to maintain therapeutic drug levels for an extended length of time, with release profiles largely controlled by the system's unique technological construction and design.

Prolonged action: - Long-term action Long-acting or prolonged-action products are dose formulations that comprise chemically modified medicinal ingredients to extend biological half-lives.[7]

Theory of Sustained Release: - The sustained-release dosage form contains:

Loading dose

Maintenance dose

The loading dose or immediately available portion achieves the therapeutic level quickly after administration, while the maintenance dose or slowly available portion releases the drug slowly and maintains the therapeutic level for an extended period.

The rate of release of the drug from the maintenance dosage should be zero order (independent of the concentration) to make the drug available constantly at the absorption site. The release of the drug from the loading dose should follow first-order kinetics.[8]

Criterion for Drug Selection of SRDDS: - The oral route of drug delivery is the most frequently used and is very convenient, safe, and simple. The scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following aspects physiochemical, pharmacokinetics, and pharmacodynamic characteristics of a drug, anatomical and physio-mechanical characteristics of GI tract, and physio-mechanical characteristics of the drug delivery mode of the dosage form to be designed. [9]

Table 1: Physicochemical and pharmacokinetic parameters for drug selection

Parameters	Criteria for drug selection
Physicochemical parameters for drug selection	-
Molecular size	< 1000 Daltons

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Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from all GI segments	Release Should not be influenced by pH and enzymes
Pharmacokinetic parameters for drug selection	Between 2 to 8 hours
Elimination half-life (t1/2)	Should be 75% or more
Absolute bioavailability	Must be higher than the release rate
Absorption rate constant (Ka)	
The apparent volume of distribution (Vd)	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on the dose
Elimination rate constant	Required for design
Therapeutic concentration (CSS)	The lower Css and smaller Vd, the loss among of drug required.
Toxic concentration	Apart from the value of MTC And MEC the dosage form

Characterization of Sustained Release Tablets: - There are number of techniques have been used to characterize SRDDS and determine the various feasibility or flexibility of their formulation process. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.[10]

Sustained-Release Tablets and Capsules: - Sustained-release tablets and capsules are commonly taken only once or twice daily, as compared with counterpart conventional forms that may have to be taken three or four times daily to attain the same therapeutic effect. [11]

Peroral Sustained Release Formulation: - Peroral sustained release formulations are defined as formulations from which the drug release is controlled over a certain period. Terms such as controlled-release, prolonged-action, repeat action and extended-release have also been used to describe such dosage forms.

Matrix Tablet: - Matrix tablets can be defined as the oral solid dosage forms in which the drug is homogeneously dispersed or dissolved within the hydrophilic or hydrophobic polymeric matrices.[12]

Classification of Matrix Tablets

Based on the retardant material used

Hydrophilic matrix tablet: - The hydrophilic matrix may be formulated by wet granulation of the drug and hydrophilic matrix materials or by direct compression of the blended mixture of active ingredients and certain hydrophilic carriers.

This is particularly true for the formulation of water-soluble drugs. Various polymers used for the preparation of hydrophilic matrices are tabulated in Table 2.

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Table 2: List of polymers used in the preparation of hydrophilic matrices

Polymer	Example
Cellulose derivatives	Hydroxypropylmethylcellulose (HPMC)25,100,4000 and 15000 cps, Hydroxyethylcellulose(HEC), Sodium carboxymethyl cellulose, and Methylcellulose 400 and 4000 cps.
Natural or semi-synthetic polymers	Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of galactose and mannose, Chitosan and Modified starches.
Polymers of acrylic acid	Carbopol 934
Other hydrophilic materials	Alginic acid, gelatin and natural gums

Hydrophobic matrices (Plastic matrix tablet):-In the plastic matrix, usually, the drug release is delayed because the dissolved drug has to diffuse through a capillary network between the compacted polymer particles. The drug can be dissolved in the plastic by an organic solvent and granulated upon evaporation of the solvent. [13] Using latex or pseudo-latex as granulating fluid to granulate the drug and plastic masses. For example: Polyvinyl Chloride, Ethylcellulose, Cellulose acetate, and Polystyrene.

Fat-wax matrix tablet :-The drug can be incorporated into fat wax granules by spray congealing in the air, blend congealing in an aqueous media with or without the aid of the surfactant and spray-drying techniques The mixture of active ingredients, waxy materials, and other additives also can be converted into granules by compacting with a roller compactor, heating in a suitable mixture such as a fluidized – bed and steam jacketed blender, or granulating with a solution of waxy material or other binders.[14]

Formulation-related factors

Formulation geometry (Size and Shape of tablet): Both the size and the shape of a tablet formulated as a matrix system exhibiting both diffusional and erosional release can affect the drug dissolution rate. Tablet matrices should be manufactured to be as spherical as possible, to produce the minimum release rate, about tablet shape.[15]

Formulation Additives: Preformulation studies of the possible interaction between excipients in the solid dosage forms are necessary because these interactions can affect the drug release and bioavailability. Addition of soluble fillers enhances the dissolution of soluble drugs by decreasing the diffusional path length, while insoluble fillers affect the diffusion rate by blocking the surface pores of the tablet. [16]

Methods of Preparation

Direct Compression: In this process, powdered materials are compressed directly without changing the properties of the drug like physical and chemical.

Wet Granulation: In this method weighed quantities of drug and polymer are mixed with sufficient volume of the granulating agent. After enough cohesiveness was obtained, the mass is sieved through 22/44 mesh. The granules are dried at 40°C and after that kept in a desiccator at room temperature. Once the granules dried are retained on 44 meshes were mixed with 15% of fines. Lubricants and Glidants are added and the tablets are compressed using a tablet compression machine.[17]

Two-step granulation method: - Two-step is a useful alternative to dry granulation. The acidic and

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basic components are separately granulated and, in the end, followed with the aid of dry mixing, before adding the lubricant for tableting. This may be finished the usage of high shear granulator. This approach requires most effective traditional gadget which may be used for granulation and drying of other materials. Alternatively, a commonplace manner is to granulate best one of the effervescent resources and add the alternative as powder shape for the durationof the final blending. Other additives like flavors and lubricants are brought to it and mixed. This method will increase productivity and reduce price by using saving the valueof a whole granulation step.[18]

One-step granulation method: - One step granulation process presented dry bubbling granules directly through granulating the acid resources and the alkaline materials together. This is carried out through using limited amount of water, which initiates but controls the bubbling reaction, for this reason forming granules.

Dry Granulation: - The powder combination is compacted without the use of heat or solvent in the dry granulation process. It is the least desirable of all granulation processes. The two main techniques are to compress the material into a compact and then mill it to obtain a granule. Two methods are used for dry granulation. Slugging is a more common procedure, in which the powder is recompressed and the resulting tablet or slug is ground to produce the granules. The other option is to use a machine like the Chilosonator to recompress the powder with pressure rolls.[19]**.**

Direct compression: -Direct compression is another alternative method for dry granulation. This was successfully used for making ready bubbling pills of acetyl salicylic acid. This facilitates in overcoming operational and stability issues throughout manner This is an ideal manner of manufacturing but its limited due to the need of requirements of sophisticated raw material aggregate (Compressible, unfastened flowing and non-segregating).

Roller Compaction: - A machine known as a chilsonator can also be used to condense powder by using a pressure roll. The chilsonator, unlike the tablet machine, produces a compressed material in a constant continuous flow. The powder is fed down between the rollers from a hopper with a spiral auger that feeds it into the compaction zone. The aggregates are screened or crushed into granules in the same way that slugs. [20]

High shear granulator: - It is the most frequent arrangement for manufacturing pharmaceutical granules on a large scale. This system, once again, allows for complete integration with upstream and downstream equipment, and even incorporates a wet mill between the granulator and the dryer. It is simple to load, mix, and granulate a second batch in the high shear granulator while drying the previous batch in the fluid bed prior to discharge with modern control systems. In a single automated operation, all equipment may be cleaned in place.

Melt Granulation: This substance can be added in the molten form over the substrate, which is then heated above its melting point. In melt granulation, meltable substance act as liquid binding agent and hence does not require the use of organic solvents. Various lipophilic binders such as Glyceryl Palmitostearate were used in melt granulation technique.[21]

Parameters

Bulk density: It is the weight of powder or granules divided by its volume. Bulk density is used to check the uniformity in bulk powdered materials, to decide the size of container, equipment's for production, size of packing material and selecting size of empty gelatine capsules.

Tapped density: It is the weight of granules divided by its tapped volume. Tapped volume is the volume of powder determined by tapping a measuring cylinder containing weighed amount of powder. The cylinder is tapped for about one minute (or 100 taps) to get constant volume.

Compressibility Index (Carr's Index): - The compressibility index (CI) is a measure of tendency of a powder to consolidate (i.e. unite to form a solid form). As such it is a measure of inter-particulate

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interactions. In a free-flowing powder, inter-particulate interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions; bridging between particles often results in lower bulk density and a greater difference between the bulk and tapped densities. These differences in particle interactions are reflected in the CI. It is important to maintain optimum followability of powders and uniform tablet weight. Lower compressibility value indicates better flow.[22]

Table 3: Standard values of the Compressibility index

S. No.	Flow Property	Compressibility index
1	Excellent	0-10
2	Good	10-15
3	Fair	16-20
4	Passable	21-25
5	Poor	26-31

Hausner's ratio: The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H.

The Hausner ratio is calculated by the formula: $\mathbf{H = \frac{Tapped\ density}{Bulk\ density}}$

A Hausner ratio greater than 1.25 - 1.4 is considered to be an indication of poor flowability. The Hausner ratio (H) is related to the Carr index (C), another indication of flowability, by the formula . Both the Hausner ratio and the Carr index are sometimes criticized, despite their relationships to flowability being established empirically, as not having a strong theoretical basis.

Table 4: Standard values of Hausner's ratio

S. No.	Flow Property	Hausner's ratio
1	Excellent	1.00-1.11
2	Good	1.12-1.18
3	Fair	1.19-1.25
4	Passable	1.26-1.34
5	Poor	1.35-1.45
6	Very Poor	1.46-1.59

Angle of Repose: The angle of repose, or critical angle of repose, of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding. The angle of repose can range from 0° to 90°. If a small amount of water is able to bridge the gaps between particles, electrostatic attraction of the water to mineral surfaces will increase the angle of repose, and related quantities such as the soil strength.[23]

Table 5: Standard values of Angle of repose

S. No.	Flow Property	Angle of Repose
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55
6	Very Poor	56-65

Evaluation Test for Sustained Release Matrix Tablets: - The evaluation parameters mentioned

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in pharmacopeias for the sustained release tablets are similar to those mentioned under conventional tablets, however, all of them stress the disintegration test.

Hardness: - Tablet hardness and strength are the essential to see that the tablet can with the shock and stress during manufacturing packing and transportation, and while handled by the patient. To test the hardness of the tablet Monsanto tester, Strong-cobbtester, thePfizer tester, the Erwekatester, the Schleuniger testers are used.

Friability:- Friability is the tested for a tablet to see whether the tablet is stable to abrasion or not, it is tested by using Rochefriabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions. The dimensions (diameter and thickness) were then determined to within ± 0.01 mm by using digital verniercalipers. and weighed (W) again. Permitted friability limit is 1 % w/w. Percentage friability was calculated from the weight loss by the following equation.[24]

In-vitro dissolution study

The release rate of matrix tablet was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml solvent and set RPM. A sample of the solution w atus at different time interval. The samples were replaced with quantity. The samples were filtered through a membrane filter. The absorbance of these solutions was measured using a UV is double beam spectrophotometer

$$\% \text{ Friability} = W0 - W/W0 \times 100$$

Material and Methods

Selection of Drug and excipient

Table 6: List of Chemicals Used

S. No	Chemicals	Company
1	Econazole	Mylan, Hyderabad.
2	Manila copal	Serin Formulations pvt.Ltd
3	Guar gum	Mylan, Hyderabad.
4	Pectin	(Standard chemicals
5	Microcrystalline cellulose	Standard chemicals
6	PVP K30	Standard chemicals
7	Talc	Standard chemicals
8	Magnesium stearate – Lubricant	Standard chemicals

Preformulation Study: - It is the initial evaluation during preformulation studies which assess the colour, odour and taste of the substance. The appearance was checked visually for colour, homogeneity andtransparency. The appearance was checked visually for colour, homogeneity and

ISSN:1624-1940
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transparency.[25]

Solubility: - Solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy. Solubility of drug was determined in different solvents.

Melting Point: - Melting point of drug was determined by Open capillary method.

Partition Coefficient: - The partition coefficient of drug was examined in n- Octanol:water system. It was determined by taking 5mg of drug in separating funnel containing 5ml of n-Octanol and 5ml buffer. The separating funnel was shaken for 2 hours in a wrist action shaker for equilibrium. Two phases were separated and the amount of drug in aqueous phase was analysed spectrophotometrically at 224 nm after appropriate dilution with buffer.

Determination of λmax: - About 5mg of Econazole was weighed and transferred into 5ml volumetric flask. The volume was made up to 5ml using methanol to obtain a solution that has a concentration 1000 µg/ml. 1ml of this stock solution was taken and then diluted up to 10 ml using methanol to obtain a solution that has a concentration 100 µg/ml which is standard stock solution.[26]

Standard calibration curve of Econazole

Determination of absorption maximum (λmax): - From the above stock solution 0.3 ml sample was transferred into a 5 ml volumetric flask and the volume was made up to mark with methanol to prepare a concentration of 6µg/ml. The sample was scanned by UV-VIS Spectrophotometer in the range of 200- 400 nm, using methanol as a blank. The wavelength corresponding to the maximum absorbance (max) was found to be 224nm.

Preparation of calibration curve: - Aliquots of 2, 4, 6, 8, 10, and 12 µg/ml were prepared utilizing 100 µg/mL econazole standard stock solution were accurately transferred into a series of 10 mL calibrated flask and made up to the mark with methanol. The absorbance of the resulting solution was measured at 224nm against methanol blank. Calibration curve was prepared by plotting the absorbance vs concentration of drug.[27]

Compatibility Study of drug and excipient: - Drug excipient compatibility was determining by the FTIR. In this work we are using FTIR for compatibility studies.[28]

FTIR: - Fourier Transform Infrared (FTIR) spectral analysis t he pure drug econazole and polymers used in this experimental work were studied for compatibility studies. We carried out these studies by taking 2 mg of sample in 200 mg of potassium bromide (PerkinElmer, Spectrum100, Japan). The range of scanning was 400-4000cm-1 and resolution was 1cm-1.[29]

Evaluation parameters: -

Tapped density: - The above procedure was followed. The final volume was tapped till no further reduction in volume was noted. Packed bulk density was determined by thefollowing formula.

$$DB = m/Vb$$

Where m =mass of granulation in gm Vb = volume of granulation (Final tapped volume).

Carr's Index: - It is expressed in percentage and is expressed by

$$6I = Dt - Db / Dt$$

Where Dt is the tapped density of the powder and Db is the bulk density of the powder.[30]

Hansner Ratio: - It is expressed in percentage and is expressed by

$$7H= Dt / Db$$

Where Dt is the tapped density of the powder and Db is the bulk density of the powder. Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones6 (>1.25).[31]

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Development of an econazole matrix tablet: - After mixing the powder with appropriate characteristics, the tablets were made. Econazole was first triturated with sweeteners and then mixed with the effervescent base. The prepared tablets were dried in an oven at 60°Cfor 1 hour. They were finally packaged.[32]

Table 7: Composition of tablet [33]

S. No.	Ingredients (mg)	Formulations					
		F1	F2	F3	F4	F5	F6
1	Econazole	80	80	80	80	80	80
2	Guargum	20	40	60	-	-	-
3	Pectin	-	-	-	20	40	60
4	Microcrystalline Cellulose	43	43	43	43	43	43
5	PVP K30	5	5	5	5	5	5
6	Talc	0.6	0.6	0.6	0.6	0.6	0.6
7	Magnesium Stearate	0.6	0.6	0.6	0.6	0.6	0.6

Matrix tablet assessment

Hardness: - Monsanto hardness tester was used to evaluate hardness of tablet. The tester consists of abarrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The upper plunger wasthen forced against a spring by turning a threaded bold until the tablet fractures. As the spring compressed, a pointer rides along a gaugein the barrel to indicate the force. The force of fracture was recorded, and the zero-force reading was deducted from it. Ten tabletsof each formulation were evaluated.[34]

Friability: - Friability of the tablets was determined using friabilator. It subjected the tablets to the combined abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping a tablet at height of 6 inches in eachrevolution. The tablets were reweighed. Tablets were de-dusted using a soft muslin cloth and reweighed. The percentage of the tablet's friability was calculated as.[35] The desirable friability was determined as lower than 1 In-vitro dissolution rate**.** The release rate of econazole from sustained release tablets was determined usingUSP Dissolution Testing Apparatus II. The dissolution medium used was 900 ml of phosphate buffer pH 7.4 which was maintained at 37±0.50C. The paddle speed was kept at 50 rpm throughout the study. Five ml of samples was withdrawn at appropriate interval and diluted to 10ml then 5ml of fresh dissolution media maintained at the same temperature was replaced. The samples were analyzed spectrophotometrically at 224 nm using phosphate buffer pH 7.4 as blank. The rawdata was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.[36]

Result and Discussion

Pre-formulation studies: - Pre-formulation studies were performed. The result is given below.

Organoleptic evaluation: - In the organoleptic evaluation of drug, colour, odour, and appearance were evaluated.

Table 8: Organoleptic evaluation of Econazole

S. No.	Parameter	Inference
1	Color	White

ISSN:1624-1940
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2	Odor	Odorless

Discussion: - From the above table it is depicted that the drug econazole is white in colour
Solubility study: - Results of the solubility studies are given below.

Table 9: solubility of econazole

S. No.	Solvent	Solubility
1	Benzene	Soluble
2	Chloroform	Sparingly soluble
3	Methanol	Soluble
4	Water	Slightly soluble
5	Acetone	Soluble

Discussion: - The drug is found to be soluble in benzene, methanol and acetone, sparingly soluble in chloroform and slightly soluble in water.

Melting point determination

Table 10: Melting point of Econazole

S. No.	Drug	Specification	Inference
1	Econazole	163-165	163˚ C

Discussion: - Melting point of econazole was found to be 163˚C.

Partition Coefficient

Table 11: Partition Coefficient of Econazole

S. No.	Solvent	Log P
1	n-octanol: water	4.75

Discussion: - Partition coefficient of the drug was found to be 4.75 in n-octanol: water.
Determination of λ max: - Solution was scanned under UV-Vis Spectrophotometer and λ max was determined. It was found to be as per the monograph.

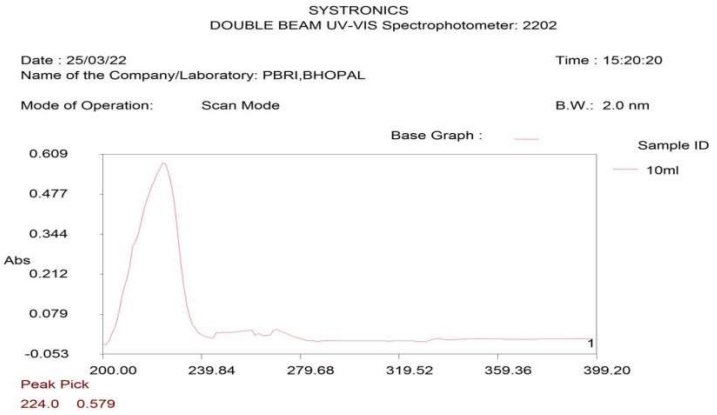

Figure 2: λmax of econazole

ISSN:1624-1940
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Standard calibration curve of Econazole

Table 12: Calibration curve of econazole

Concentration (µg/ml)	Absorbance (224 nm)
2	0.128
4	0.229
6	0.318
8	0.409
10	0.535
12	0.669

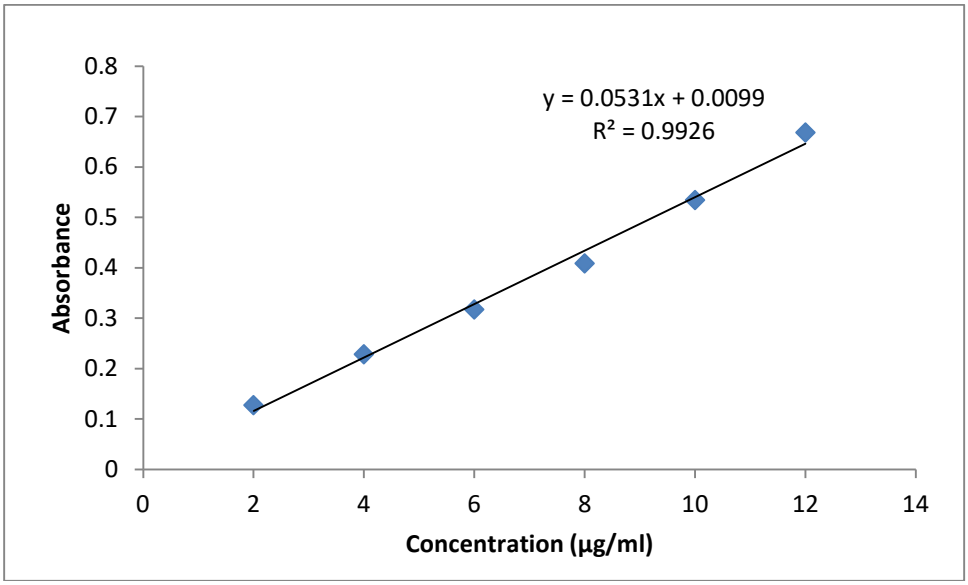

Figure 3: Calibration curve of econazole

Drug and excipients compatibility studies

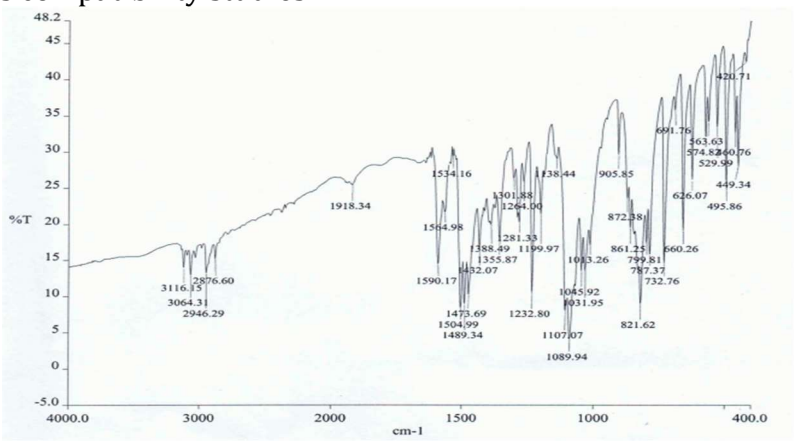

Figure 4: FTIR of econazole

Table 13: Interpretation of IR spectra

S. No.	FTIR peaks obtained	Standard range	Functional group
1	3116.15	3550 – 3200	O-H and N-H associated

ISSN:1624-1940
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			with hydrogen bonding
2	3064.31	3100 – 3000	Alkene =C-H stretching
3	2946.29	2990 – 2850	Alkane C-H stretching
4	1590.17	1700 – 1500	C=O stretching
5	1534.16	1650–1580	N-H stretching
6	1199.97	1320–1000	C-O ether
7	1432.07	1625 – 1440	Aromatic C=C stretching
8	660.26	600 – 840	C-Cl stretching

Powder Property

Flow property of the granules was performed by different parameters like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio and the results are given below.

Table 14: Results of flow property of granules

Flowability property	**Formulations**				
	F1	**F2**	**F3**	**F4**	**F5**
Angle of repose	23.46	24.64	23.75	25.46	26.57
Bulk Density	0.746	0.537	0.648	0.856	0.645
Tapped density	0.227	0.235	0.326	0.345	0.265
Compressibility index	24.75	25.46	24.55	26.28	25.84
Hausner´s ratio	1.16	1.14	1.17	1.15	1.18

Discussion: Powder blends were evaluated for different precompression parameters and the results are mentioned in table:15.

Angle of Repose: - Angle of repose of econazole powder blend was found in the range of 23ºto 26°. These values are well within the limit of 25º – 30° which indicates the flow of econazole was excellent. The above results revealed that the all the formulations (F-I to F-5) possess excellent flow.

Bulk Density and Tapped Density: - Bulk density of econazole was found between 0.53 to 0.85 g/cm3. Tapped density ranges between 0.22 to 0.34 g/cm3.

Compressibility Index and Hausner's Ratio: - Compressibility index values was found to be in the range of 24.55 to 26.28 % and the hausner,s ratio lies between 1.14 to 1.18.

Econazole Matrix tablet assessment: - Evaluation of the different batches of the tablets was performed for hardness, friability test, and weight variation. Disintegration time and % drug content. The results are given below.

ISSN:1624-1940
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Table 15: Results of post-compression evolution

Evaluationparameters	Formulations				
	F1	**F2**	**F3**	**F4**	**F5**
Hardness (Kg/cm^2)	5.200	4.500	5.000	4.700	5.300
Friability %	0.369	0.478	0.385	0.538	0.583
Weight variation (gm)	2.17	2.84	1.19	2.04	1.16
Disintegration time (minutes)	71	73	68	69	75
Drug content %	97.47	95.48	98.46	96.84	95.67

Hardness(kg/cm^2): - The hardness test carried out was by using monseto tester. The hardness values of formulations (F-I to F-5) were found to be in the range of 4.5 to 5.3 respectively. Hence all the tablets passed the hardness test.

Weight Variation Test: -Five tablets of each formulation were randomly selected for weight variation test. The accepted percentage deviation was ± 7.5 for 130 – 324 mg tablet weight as per I.P. The results showed that the weight of tablets ranges from 1.16 to 2.84 for all formulations well within the I.P limit (± 7.5). Hence all the tablets passed the weight variation test.

Friability Test: - The friability test is carried out by using Roche friabilator. The maximum weight loss should not be more than 1%. The friability values of formulations (F-I to F-5) were found to be 0.36 to 0.58 respectively. Hence all the tablets passed the friability test.

Drug Content: -The content uniformity of formulation 1 to formulation 5 was found to be in the range of 95.48 to 98.46. Hence all the tablets passed the content uniformity test.

Table 16: *In vitro* evaluation percentage of drug release

Time in hours	Formulations (%)				
	F1	**F2**	**F3**	**F4**	**F5**
2	15	18	16	20	13
4	24	27	28	31	22

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6	38	41	36	45	35
8	45	58	54	62	48
10	70	78	75	74	65
12	84	85	84	83	81
24	94	95	98	96	90

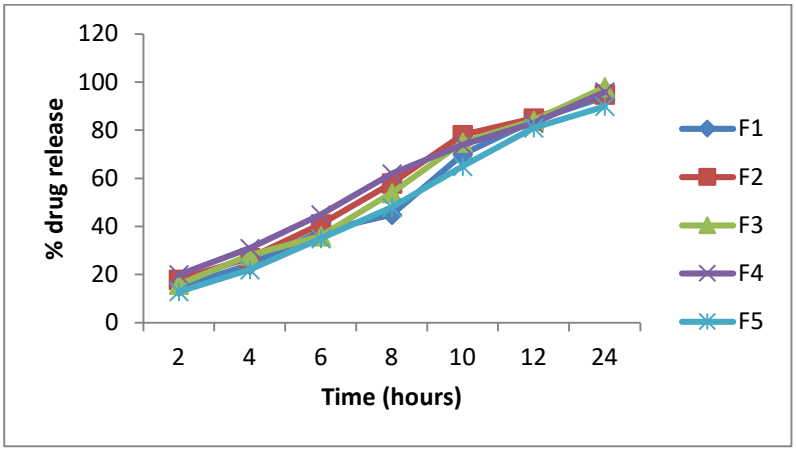

Figure 5: Cumulative % drug release

Discussion: - *In vitro* drug release profiles for all formulations were carried out by using 7.4 pH phosphate buffer as dissolution medium for about 24 hrs. From the above results it was found that the release of drug from formulation F3 gave the better release.

Kinetic studies: - Since formulation F3 showed highest drug release so it was selected for the kinetic studies.

Table 17. Release kinetics study of F3 formulation.

Formulation	Model	Kinetic parameter values
F3	Zero Order	$y = 3.825x + 19.78$ $R^2 = 0.816$
	First Order	$y = -0.077x + 2.182$ $R^2 = 0.983$
	Higuchi	$y = 22.78x - 8.710$ $R^2 = 0.918$

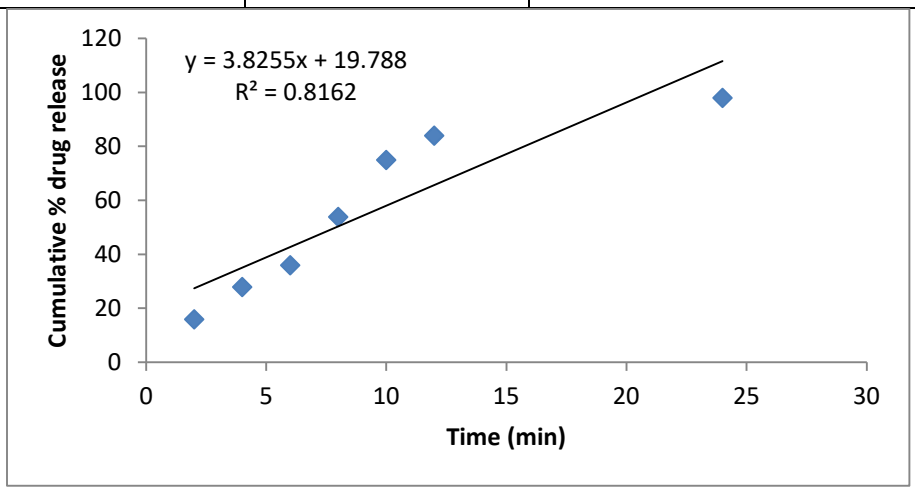

Figure 6: Zero order model of F3 formulation

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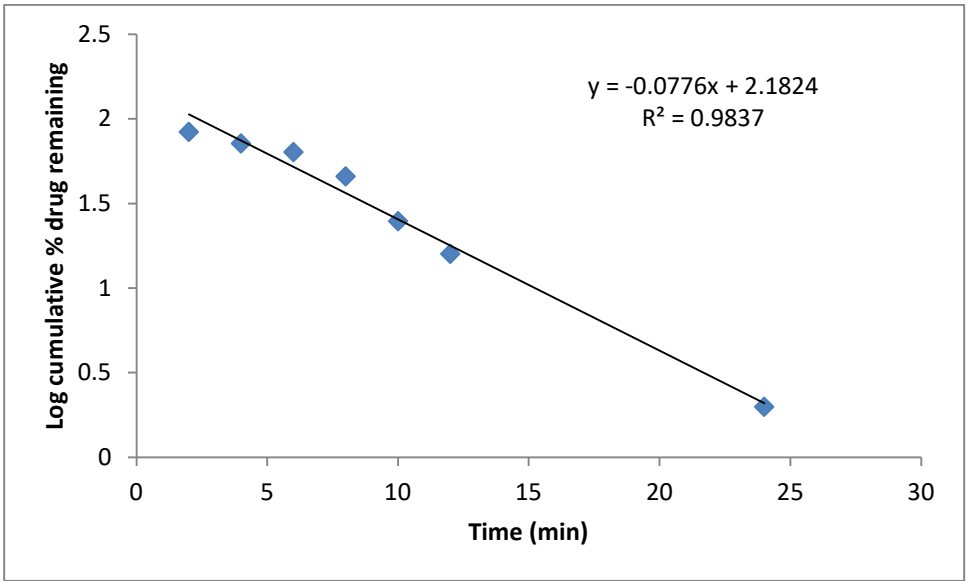

Figure 7: First order model of F3 formulation

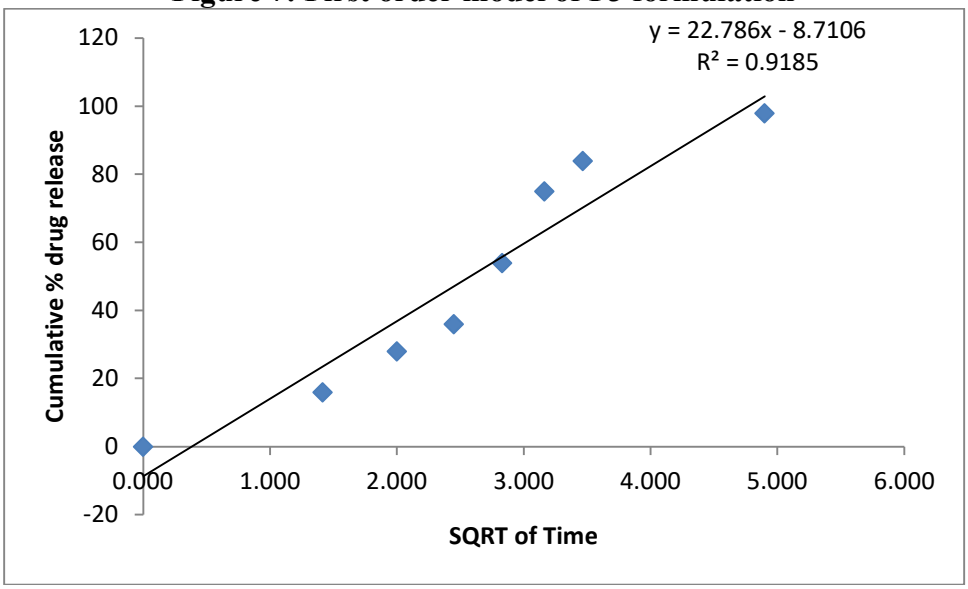

Figure 8: Higuchi model of F3 formulation

Discussion: - Zero order kinetic model refers to the process of constant drug release from a drug delivery device independent of the concentration. The zero-order graph of F3 formulation showed the constant drug release from the tablets, the results of the zero-order model was found to be y =3.825x + 19.78, R2 = 0.816. The first-order kinetic model describes the release from a system where the release rate is concentration-dependent. The results of first order kinetic model were found to be y =-0.077x + 2.182, R2 = 983. The Higuchi model is used to describe the limits for transport and drug release. The Higuchi model of tablets was found to be y =22.78x - 8.710, R2 = 0.918.

Summary and Conclusion Sustained release tablets of econazole were prepared by compressing granules that were successfully prepared by wet granulation method with guar gum and pectin as binders and other excipients like microcrystalline cellulose, PVP K30, Talc, and Mg-stearate. Preformulation studies of the drug were performed first and the results were found to be the drug is white in color and odourless. The solubility of the drug was found to be soluble in benzene, methanol,

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and acetone, sparingly soluble in chloroform, and slightly soluble in water. The melting point and partition coefficient were determined by open capillary method and phase separation method. The melting point and partition coefficient of the drug were found to be 163˚ C and 4.75. The UV absorbance of econazole standard solution in the range of 10-50 µg/ml of drug in Methanol showed linearity at λ max 224nm. The linearity was plotted for absorbance against concentration with R^2 value 0.992 and with the slope equationy=0.053x + 0. 009. The compatibility between the drug and other Excipients was evaluated using FTIR peak-matching method. There was no appearance or disappearance of peaks in the drug excipient mixture, which confirmed the absence of any chemical interaction between the drug, and other chemicals. A granule prepared by wet granulation was subjected to the evaluation of their flow property like the angle of repose, bulk density, tapped density, carr's index, and Hausner's ratio. The results were found to be in the limits. After mixing the powder with appropriate characteristics and flow properties, tablets were made by direct compression method in a single punch machine. All the prepared tablets were evaluated for test like hardness, friability, weight variation, disintegration time, drug content and dissolution studies. Hardness friability was found to be within limits. According to the European Pharmacopoeia standard for sustained-release tablets, the disintegration time should not be less than 60 min. All the formulations were disintegrated within these limits but the formulation F3 disintegrated in 68 min; it concluded that theF3formulation was found to be the best one. *In-vitro* drug release studies were evaluated for drug release by using a USP dissolution test apparatus, F3 formulation showed 98% drug release among all the formulations within 24 hours. It concluded that F3 formulation showed good in-vitro dissolution as well as disintegration. This study confirms that econazole can be successfully prepared in the form of sustained release tablets by compressing granules that were prepared by wet granulation method with excipient

Sustained release matrix tablets of econazole formulation system include the drug delivery system that achieves slow and extended release of the drug over an extended period. Sustained-release tablets of econazole have been successfully formulated using guar gum and pectin as drug-release modifiers. The findings of the present study demonstrate that the hydrophilic matrix of econazole alone could not control the release effectively for 24 h, whereas, when combined with Guar gum, it could slow down the release of the drug from their matrices and can therefore be successfully employed for formulating SR matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release, which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional econazole tablets.

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