DESIGN AND *IN VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS CONTANING DEXLANSOPRAZOLE

K.S. Srilatha[1]*, Dr. S.C. Marapur, [2]Shalini B.[1], Ajmal V.T.[1] Amal Mirshad[1], Ankit Kumar[1] and Muhammed Unais T.[1]

[1]Department of Pharmaceutics, RR College of Pharmacy Bangalore.
[2]Professor and Head of Department of Pharmaceutics, BLDEA'S SSM College of Pharmacy and Research Centre Vijayapura.

*Corresponding Author: K.S. Srilatha
Department of Pharmaceutics, RR College of Pharmacy Bangalore.

ABSTRACT

Treatment of Gastroesophageal reflux disease with conventional dosage forms is not effective as the drugs do not reach the site of action in appropriate concentration and it is also requiring dosing. Thus, an effective and safe therapy for gastroesophageal reflux disease using specific drug delivery system is a challenging task to the pharmaceutical technologists. Most used method of modulating the drug release is to include it in a matrix system, because of their flexibility, hydrophilic polymer matrix system is widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The aim of the present study was to develop and evaluate controlled release matrix tablets of Dexlansoprazole. The tablets were prepared by direct compression method and by using different concentration of polymers. Six such formulations were made using HPMC and Carbopol as polymer. Compatibility of drug with various excipients was studied by FTIR spectroscopic studies. The preformulation studies showed good flow properties and compressibility index. The compressed tablets were evaluated for various parameters like hardness, weight variation, thickness, friability, uniformity of drug content and *invitro* drug release. *Invitro* release was carried out using USP type-2 at 50rpm in 900ml of phosphate buffer pH 6.8 for 8 hours. Drug release studies indicate that increase in concentration of polymer prolongs the release rate of drug from the results obtained, F4 was selected as best formulation based on physicochemical parameters and *invitro* drug release. The results indicated that the prepared sustain release matrix tablet of Dexlansoprazole could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

KEYWORDS: Dexlansoprazole, Matrix tablets, proton pump inhibitor and gastro esophageal reflux disease.

INTRODUCTION

Matrix drug delivery systems

The dictionary meaning of matrix is a) Content or framework and b) The rock in which fossils or pebbles are embedded. The active pharmaceutical ingredient is embedded or entrapped in a network formed by polymers called matrix. Within the scope of this general term, there are a variety of controlled-release devices. Included among these are dissolved systems that are prepared from matrix containing a drug at or below its saturation solubility in the polymer and dispersed systems that contain the drug within a matrix at a concentration that greatly exceeds the saturation solubility of the drug in the polymer. Other controlled-release devices include reservoir dispersed matrix systems, which are analogous to the dispersed system except that barrier layer is present at the surface of such device.

Mechanism of drug release from matrix-drug delivery system.

Dissolution of the drug on the surface

Depletion of the drug closer to the surface by diffusion

Elution of the drug present in the next layer by diffusion through the matrix The release of a drug from matrix devices is governed mainly by diffusion of the solute within the matrix phase. The development of appropriate release-rate equation is generated via Fick's first law of diffusion.

Matrix Tablets

In these systems the drug is homogenously dispersed in the polymeric matrix, mixed along with other excipients and compressed into tablets. A variety of polymers like

hydrophilic, hydrophobic, waxes, gums etc. could be incorporated alone or in combination in order to prolong the drug release.

There are three types of matrix tablets i.e.
1. Hydrophilic matrices
2. Fat-wax matrices
3. Plastic matrices

Examples of different types of matrices

Types of matrices	Examples
Hydrophobic matrices (Plastic matrices)	Polyvinylchloride, Ethyl cellulose, Methycrylate methyl acrylate copolymer, polyethylene
Lipid matrices	Stearyl alcohol, stearic acid, triglycerides, carnauba wax and polyethylene glycol
Hydrophilic matrices	Methylcellulose, Carboxypolymethylene, hydroxypropyl methylcellulose (HPMC).

Requirements of matrix material:
The matrix materials must comply with the following conditions
- They must be non-toxic.
- They must be completely inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices when compressed either directly or more often granules prepared by the addition of binding agent.[1]

a) Hydrophobic Matrices (Plastic matrices)
The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining controlled release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Controlled release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compactable polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethylcellulose and acrylate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

b) Lipid Matrices
These matrices are prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulations.

c) Hydrophilic Matrices
The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. In fact a matrix is defined as well mixed composite of one or more drug with gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.[2]
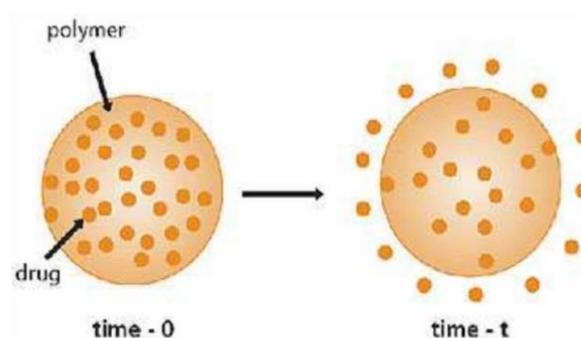

Figure 1: Schematic representation of diffusion sustained drug release matrix system.

Gastroesophageal reflux disease (GERD) is a chronic symptom of mucosal damage caused by stomach acid coming up from stomach into the esophagus. GERD is caused by the changes in barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter. The most common symptoms include heart burn and regurgitation as shown in figure 1. Medications such as proton pump inhibitors, H_2 receptor blockers and antacids are used in the treatment of GERD. DSP is a proton pump inhibitor drug used in the treatment of GERD. However, it is degraded in acidic stomach pH, thus lacking in pharmacological action of the drug. GERD is a common condition with a prevalence of 10–20% in the Western world and an annual incidence of 0.38–0.45%. The range of GERD prevalence estimate is 18.1–27.8% in North America and 8.8–25.9% in Europe. In the United States (US), 20% of the population experience GERD related symptoms weekly and 7% daily. Several studies have demonstrated that patients with GERD have reduced health-related quality of life and work productivity.
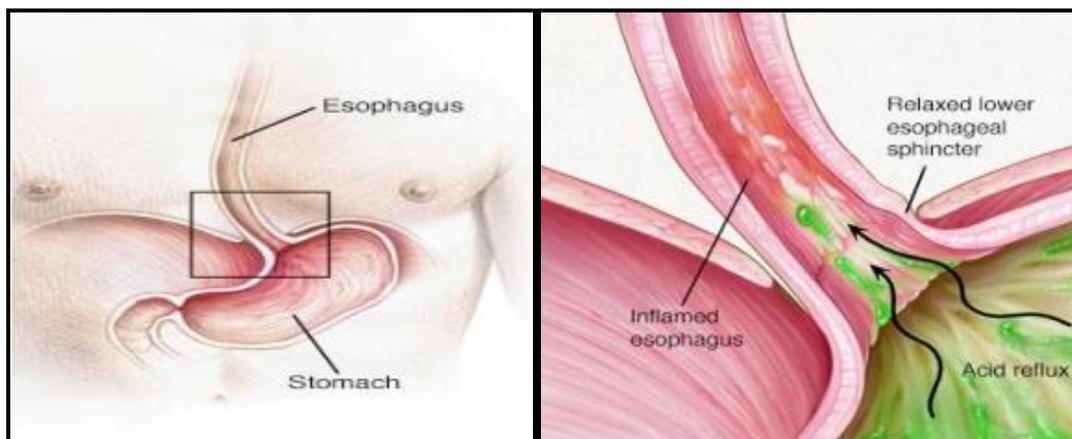
Figure 2: Heart burn and GERD occur.

Dexlansoprazole is a medication which reduces stomach acid. So, it is used to treat gastroesophageal reflux disease. Dexlansoprazole is a new generation PPI used for the management of symptoms associated with GERD and erosive esophagitis. Dexlansoprazole is used to heal and maintain healing of erosive esophagitis and to treat heartburn associated with GERD.[3]

MATERIALS AND METHOD
Dexlansoprazole was supplied as a gift sample from Sri Krishna Pharma, HPMC and Magnesium Stearate was obtained from Yarrow chem products Mumbai, Carbopol was obtained from Balaji drug Bangalore. Lactose and Dibasic calcium phosphate anhydrate was obtained from SD Fine chemical limited, Talc was obtained from Central drug house (Pvt) Ltd.

Determination of standard calibration curve of Dexlansoprazole using phosphate buffer pH 6.8
A stock solution of 1mg/ml of Dexlansoprazole was prepared by dissolving 100 mg of drug with phosphate buffer in 100 ml volumetric flask. The stock solution was serially diluted to get solutions in the range of 5-25µg/ml.
The absorbance solution was measured in a UV-Visible spectrophotometer at 285nm. A calibration curve was plotted by taking concentration of solution in X axis and absorbance in Y axis and correlation coefficient 'r^2' was calculated.[3]

FT-IR Spectroscopy
This study was carried out to find the compatibility in between the drug and the various excipients, which was used in the formulation of a dosage form.

Procedure
- The sample disc was prepared by triturating approximately 1 or 2 mg of the sample substance with around 10 – 20 mg of Kbr / potassium bromide and the triturate is compressed by a hydraulic press in order to form a thin disc of around 10-15mm diameter, which will be sufficient to give an IR spectrum of a suitable intensity.
- This disc was then placed in a sample holder and it is scanned in the range of 4000-400cm^{-1} in a FTIR spectrophotometer in order to get a spectrum.
- The obtained spectra of drug and the excipients were compared and it was interpreted for the functional group peaks in order to check for any major interactions.[4]

FORMULATION TABLE OF THE DEXLANSOPRAZOLE TABLETS
Table 1: Composition of matrix tablets of Dexlansoprazole.

SL.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
1	Dexlansoprazole (mg)	60	60	60	60	60	60
2	HPMC K 100M (mg)	80	70	60	_	_	_
3	Carbopol-934 (mg)	_	_	_	80	70	60
4	Lactose (mg)	50	60	70	50	60	70
5	Talc (mg)	5	5	5	5	5	5
6	Magnesium sterate (mg)	5	5	5	5	5	5

Preparation of matrix tablets of Dexlansoprazole
- The tablet containing 60mg of Dexlansoprazole along with various amount of the polymers such as carbopol-934, HPMC K100M, and other excipients lactose, talc and magnesium stearate were used and tablets were prepared by direct compression technique.
- Polymers were passed through mesh no.40
- In the first step, the drug and ingredients with exception of magnesium stearate was mixed for 5 minutes.

- Then magnesium stearate was added and mixture was triturated for an additional 2 minutes.
- Tablets were compressed using 4mm round flat punches on 10-station rotary tablet compression machine. Matrix tablet with a total weight of 200mg/tablet.
- Before compression, the surface of the die and punch were lubricated with magnesium stearate
- The compressed tablets were evaluated for various parameters viz. appearance, thickness, diameter, hardness, friability, weight variation, drug content and *in-vitro* drug release studies.

Figure 2: Formulated Dexlansoprazole matrix tablets.

All the preparations were stored in airtight containers at room temperature for further studies.

EVALUATION
Micrometric properties
a) Angle of repose
The angle of repose of powder was determined by the fixed funnel method. The accurately weighed powder was taken in a funnel. The powder was allowed to flow through funnel freely onto the surface in such a way that tip of funnel does not touch the heap of powder. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.[5]

$$\tan \theta = h/r$$

b) Bulk density
Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 100ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted and calculated by using formulas.

Bulk density = weight of powder / bulk volume of powder
Tapped density=weight of powder/tapped volume of powder

c) Compressibility index and Hausner's ratio.
The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the hausner's ratio are determined by measuring both the bulk volume and the tapped volume of a powder.[6]

Compressibility Index (%) = (TBD – LBD) × 100 / TBD
Hausner's ratio = TBD / LBD

II) Physicochemical parameters
a) Tablet hardness
The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.[7]

b) Tablet thickness
Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauge on 3 randomly selected samples.

c) Friability
Friability is the measure of tablet strength. Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 min dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, the tablets were re-weighed and the percentage loss in tablet weight was determined.[8]

% Loss = initial wt. of tablets – final wt. of tablets / initial wt. of tablets × 100

d) Weight variation
Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated.

e) Uniformity of drug content five tablets from each formulation were powdered individually and a quantity equivalent to 60mg of Dexlansoprazole was accurately weighed and extracted with a suitable volume of 6.8 pH buffer. Each extract was suitably diluted and analysed spectrophotometrically at 285nm.[9]

f) Drug release kinetic from the sustained release matrix tablet dosage forms
In vitro release studies were carried out using USP dissolution apparatus (Type 2). The dissolution medium consisted of 900ml phosphate buffer pH 6.8. The rotation of paddle was fixed at 50rpm and the temperature 37 ± 0.5^0C was maintained throughout the experiment. Samples of 5ml were withdrawn at predetermined time intervals and were replaced with same volume of fresh dissolution media after each with drawn. The samples

were filtered through Whatman filter paper and analysed after appropriate dilution by UV –Visible spectrophotometer at 285 nm.

Drug release from matrices usually implies water penetration in the matrix, hydration, swelling, and diffusion of the dissolved drug. Several kinetics models relating to the drug release from matrices, selected from the most important mathematical models were used.[10]

g) Stability studies
Stability testing of drug products begins as a part of drug discovery and ends with the Demise of the compound or commercial product. The stability studies were carried out of the most satisfactory formulation. The most Satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at $40 \pm 2°C/75 \pm 5\%$ RH for three months. At the end of studies, samples were analyzed for various parameters.[11]

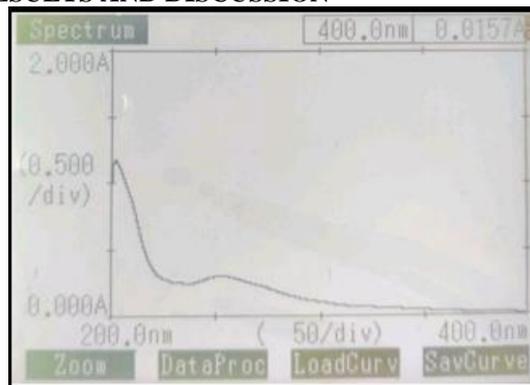**RESULTS AND DISCUSSION**

Figure 3: λ max of Dexlansoprazole in 0.1N Hcl.

Standard graph was determined in 0.1N Hcl, λ max of found to be Dexlansoprazole in 238nm with y=0.0351x+ -0.00048 and $R^2 = 0.9992$.
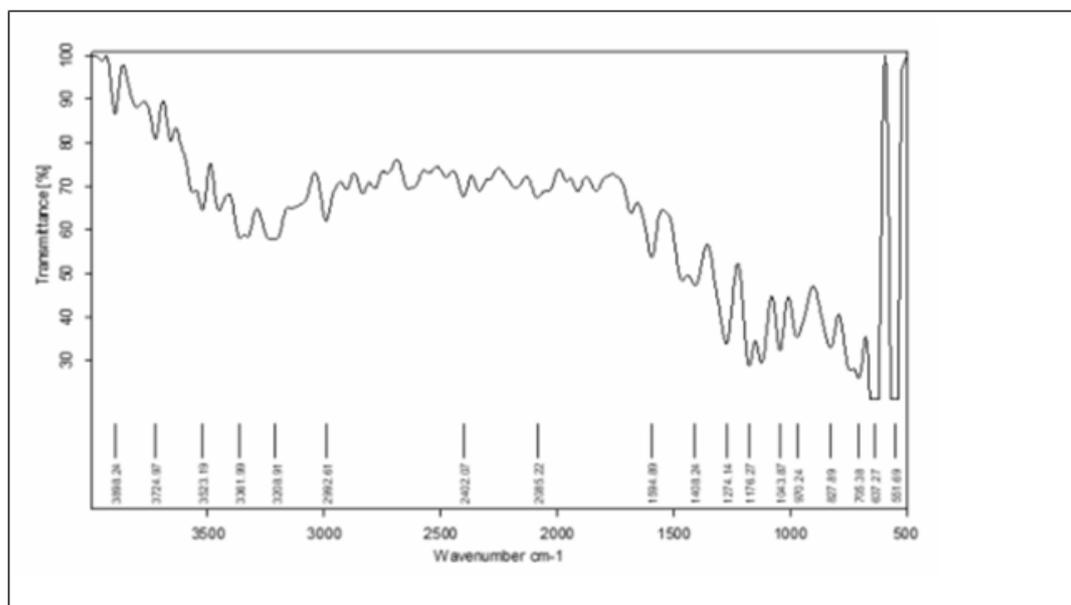

Figure 4: FT-IR spectrum of Dexlansoprazole.

Table 2: FT-IR spectrum details of Dexlansoprazole.

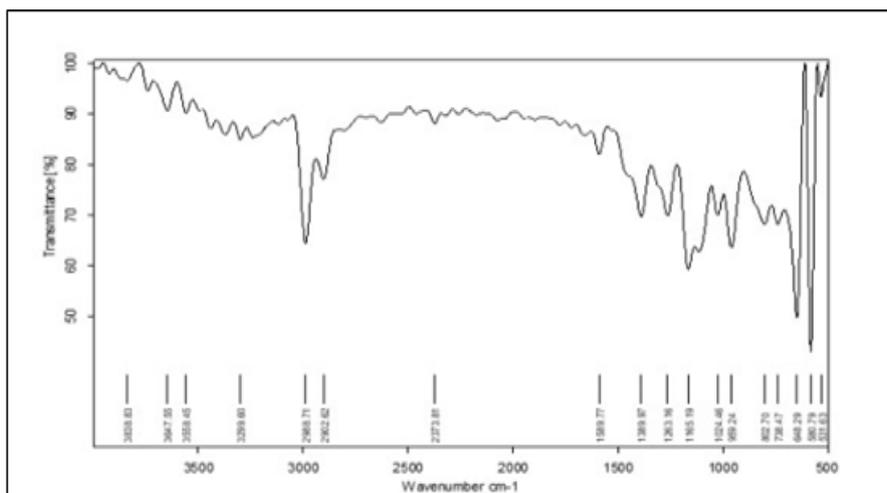| FUNCTIONAL GROUP	FREQUENCY (cm^{-1})
NH stretching	3523.19
S=O stretching	1043.87
C-S stretching	637.27
C-F stretching	1176.27
C-N stretching	1274.41
CH stretching hetero aromatic	2992.61
C-C stretching phenyl	1408.24
C-C bending	705.38

Figure 5: FT-IR spectrum of Dexlansoprazole + HPMC.

Table 3: FT-IR spectrum details of Dexlansoprazole + HPMC.

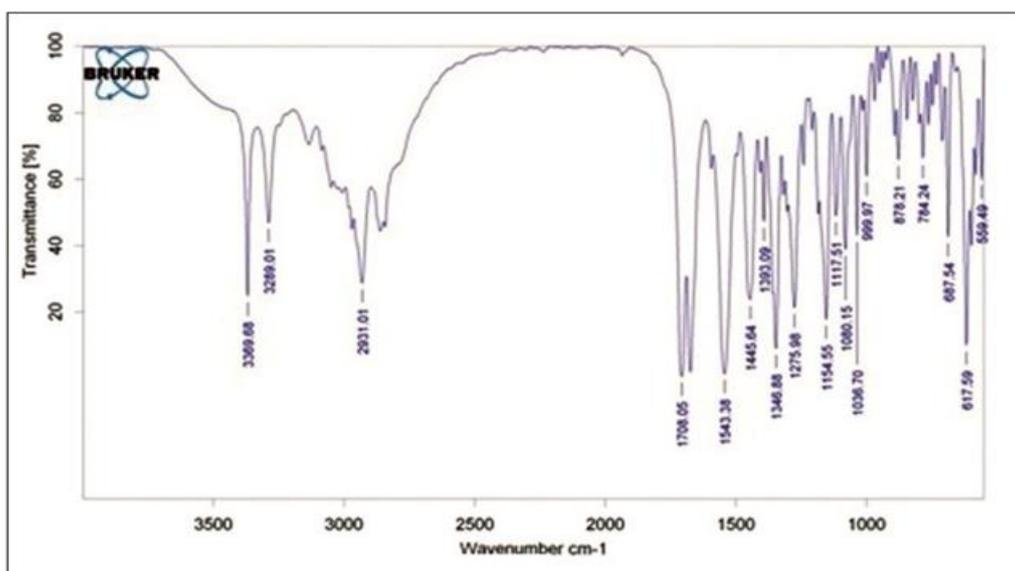| FUNCTIONAL GROUP	FREQUENCY(cm^{-1})
NH stretching	3558.45
S=O stretching	1024.46
C-S stretching	648.29
C-F stretching	1165.19
C-N stretching	1263.16
CH stretching hetero aromatic	2988.71
C-C stretching phenyl	1389.97
C-C bending	738.47

Figure 6: FT-IR spectrum of Dexlansoprazole + Carbopol.

Table 4: FT-IR Spectrum details of Dexlansoprazole + Carbopol.

FUNCTIONAL GROUP	FREQUENCY (cm^{-1})
C-F (stretching trifluoro)	1111.03
C-H (stretching hetero aromatic ring)	2970.48
C-S (stretching)	615.31
S=O(stretching)	1037.69
NH (stretching)	3408.33
C-C(stretching aromatic ring)	1440.87
C-C (bending aromatic ring)	742.62

PRECOMPRESSION PARAMETERS FOR FORMULATION F1-F6
Table 5: Evaluation of pre-compression parameters.

Formulation code	Angle of repose (^{0})	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index %	Hausner's ratio
F1	28.94	0.609	0.66	11.06	1.093
F2	27.61	0.57	0.64	11.41	1.131
F3	24.3	0.612	0.68	10.06	1.112
F4	29.19	0.55	0.616	10.05	1.11
F5	27.8	0.54	0.625	13.12	1.15
F6	25.86	0.58	0.655	10.6	1.118

Pre compression data were in the range of angle of repose 24.3 - 29.19°, bulk density 0.55 -0.612 g/cm^3, tapped density 0.616 - 0.68 g/cm^3, Carr's index 10.05 - 13.12 % and Hausner's ratio 1.093 - 1.131 all the parameter were in limits specified.

POST COMPRESSION PARAMETERS FOR FORMULATION F1-F6
Table 6: Evaluation of post compression parameters.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	5	5.3	0.28	200	97.9%
F2	5.2	5.1	0.28	190	99.33%
F3	5	4.6	0.26	200	83.9%
F4	5.1	5.7	0.24	210	99.3%
F5	5.1	5.4	0.30	200	94.30%
F6	5	5.1	0.27	200	95.44%

Post compression data were in the range of Thickness 5-5.2 mm, Hardness 4.6-5.7 kg/cm^2, Friability 0.24-0.28%, Weight variation 190-210 mg and Drug content 83.9-99.3%.
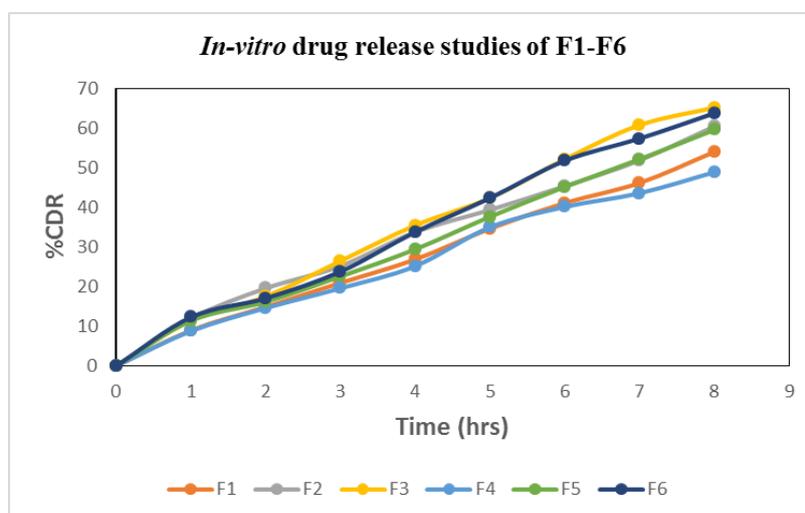
Figure 7: *Invitro* drug release studies of F1-F6.

Invitro dissolution study are carried out by using phosphate buffer pH 6.8 as dissolution medium and samples were withdrawn at every 1hr time intervals and the same was quantity of sample was replaced up to 8hrs. All the formulations released above 48% and F4 was releasing the drug in sustained manner. Hence based on all parameters obtained F4 was selected as best formulation and further kinetic models were fitted for F4 formulation.

Table 8: Kinetics Modeling Data.

Formulation	Zero order		First order		Higuchi model		Korsmeyer Peppas	
	R^2	Slope 'n' value	R^2	Slope 'n'value	R^2	Slope 'n' value	R^2	Slope 'n' value
F4	5.4244	5.424	0.9311	0.1025	0.9912	6.106	0.9311	0.1025

Kinetic data indicates that F4 follows first order reaction as R^2 values are greater in first order kinetics. Higuchi model indicated that the drug was diffused through the matrix. Korsmeyer Peppas mechanism of release was non Fickian transport.

Table 9: Accelerated study data for F4 formulation.

F4	Initial day	30 days
Weight variation(mg)	210	200
Hardness(kg/cm^2)	5.7	5.3
Drug content	99.3	98.6

Table 10: *Invitro* release data for F4 during Accelerated stability studies.

Time (hrs)	Initial day	30days
1	8.8	7.6
2	14.66	12.8
3	19.67	18.7
4	25.25	24.7
5	35.02	33.8
6	40.16	39.8
7	43.6	45
8	48.9	51.8

Accelerated stability studies was carried for one month and the results indicated that the formulation was stable for 1 month of study.

CONCULSION
The basic goal of research was to design sustain release matrix delivery system using Dexlansoprazole as model drug to reduce the dosing frequency, reduce dose, so as to maintain the therapeutic blood levels uniform for extended period of time, increase effectiveness and efficacy with minimum side effects of the drug. FTIR spectrum obtained for drug with excipients showed characteristics peaks of drug at their respective wavelength with no major shifts indicating drug and excipients were compatible. The sustain release matrix tablets were prepared by direct compression method and formulated using different polymer ratio, totally 6 formulations were prepared.

Formulations were subjected for pre compression and post compression parameters. Pre compression parameters were determined to analyse the flow properties which includes angle of repose, bulk density, tapped density, Hauser's ratio and compress ability index. The result of pre compression parameters showed good flow properties and compress ability.

Post compression parameters such as physical appearance, thickness, weight variation, hardness, friability, and *invitro* drug release kinetics study, were all in limits specified. F4 sustained the drug release for a longer period. Hence F4 was considered as the best formulation

The short term stability studies at 40 ± 2^0C/75 $\pm$ 5% relative humidity for 1 month was carried on best formulation and there were no significant changes were observed. Hence the prepared sustain release tablets of Dexlansoprazole may be good choice for preventing ulcers, GERD and erosive esophagitis.

REFERENCES
1. Vyas SP, Khar RK. Controlled drug delivery: concept and advances. 1st ed. Delhi: Vallabh Prakashan; 2002.
2. Lechman, L., Liberman, H.A., Kanig, J.L., In., The Theory and Practice of Industrial Pharmacy, 3rd Ed., Varghese Publishing House, Bombay, 1987; 430-453.
3. Vinitha, K.S. Srilatha, Dr. A Geethalakshmi. Formulation and evaluation of Oral floating Dexlansoprazole *in situ* gel for gastro phageal reflux disease by ion activated method by Journal of Fundamental and comparative research, 2021; 11(1): 33-41.
4. K.S. Srilatha, Dr A Geethalakshmi. Design and *In-vitro* evaluation of controlled release matrix tablets of Prazosin. American Journal of pharmacy and health research, 2020; 8(7): 1-11.
5. Borguist P, Korner A, Larsson A: A model for the drug release from a polymeric matrix tablets –effect of swelling and dissolution. J controlled release, 2006; 113: 216-225.
6. Ganesh GNK. Preparation and evaluation of sustained release matrix tablet of Diclofenac sodium using natural polymer J pharma Sci Res., 2010; 2(6): 360-368.
7. Kamalakkannam V, Sivaprakash R. Design and development of sustained release matrix tablets of Tramadol hydrochloride are using gum kondabolu as a natural polymer Sch. Acad. J pharma., 2015; 4(3): 199-207.
8. Hare Krishna R, Chandan K. Formulation and design of sustained release matrix tablets of Metformin hydrochloride influence of hypromellose and polyacrylate polymers int J Appl Bas Med Res., 2013; 3(1): 55-63.
9. K.S. Srilatha, T.B. Savatri, S.K. Kavitha Preparation and *in-vitro* characterization of sustained release Metformin HCL matrix tablets using different polymers world Journal of Pharmacy and Pharmaceutical sciences, 2019; 8(5): 71-80.
10. Katare VB, Bhutkar MA. Formulation and evaluation of sustained release matrix tablets of Pregabalin Res J Pharm tech, 2013; 6(11): 1190-1194.
11. Rita B, Suresh V. Formulation and evaluation of sustained release matrix tablets of Nifedipine, A clin Lab res., 2021; 9(7).