



FORMULATION AND EVALUATION OF DEXLANSOPRAZOLE CONTROLLED RELEASE TABLETS

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ABSTRACT

The aim of the present work is to formulate and evaluate controlled release of Dexlansoprazole matrix tablets used for treatment of gastroesophageal reflux disease (GERD). Development of CR Dexlansoprazole is proposed considering the adverse event profile and high fluctuation index of Dexlansoprazole observed with CR dosage forms. Dexlansoprazole was subjected to Preformulation studies, based on the results obtained Dexlansoprazole controlled release tablets were successfully formulated. Formulations prepared by direct compression technique. Set of trials were formulated for which Dexlansoprazole evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in pH 6.8 phosphate buffer. From the results of the *in vitro* study, it appears that the release of the Dexlansoprazole was significantly influenced by the characteristics of the polymer used.

Key words:

Dexlansoprazole, polymers, FTIR studies, Direct compression technique, *in vitro* drug release studies.

1.INTRODUCTION

Oral administration of drugs is the most common and preferred route for delivery of therapeutic agents. The popularity of the oral route is due to patient compliance, ease of administration, accurate dosing, cost-effective manufacturing methods, and generally improved shelf-life of the product.¹ The rationale for development of controlled release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effects. The first commercially developed oral controlled release formulation was the pellet filled capsule called Spansules which was introduced in the year 1950 by Smith, Kline and French². These were formulated by coating a drug onto nonpareil sugar beads and further coating with glyceryl stearate and wax. Since then, number of strategies were developed to obtain controlled release of a drug in the body.³ They vary from simple matrix tablets or pellets to

more technologically sophisticated controlled release systems which have been introduced into the marketplace.⁴ Successful formulation of a controlled release dosage form usually involves consideration of many factors such as the physicochemical properties of the drug, physiological factors and manufacturing variables. Reduction in frequency of drug administration, Improved patient compliance, Reduction in drug level fluctuation in blood. Reduction in total drug usage when compared with conventional therapy, Reduction in drug accumulation with chronic therapy.⁵ Limitations Delay in onset of drug action. Possibility of dose dumping in case of a poor formulation strategy. Increased potential for first pass metabolism. Greater dependence on GI residence time of dosage form.⁶ The aim of the present work is to formulate and evaluate controlled release of Dexlansoprazole matrix tablets used for treatment of gastroesophageal reflux

disease (GERD). Development of CR Dexlansoprazole is proposed considering the adverse event profile and high fluctuation index of Dexlansoprazole observed with CR dosage forms.

Drug excipient compatibility studies⁷

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were

exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change

2.MATERIALS AND METHODS

Dexlansoprazole was collected as a gift sample from Hetero labs, Hyderabad and various excipients and polymers were purchased from AR chemicals, Hyderabad.

2.1 METHODOLOGY

Formulation Development

Table-1: Formulation table of Dexlansoprazole controlled release tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	Dexlansoprazole	50	50	50	50
2	HPMC	25	50		
3	Eudragit RS 100	-	-	25	50
4	Microcrystalline Cellulose	120	95	120	95
5	Magnesium stearate	3	3	3	3
6	Talc	2	2	2	2
7	Total weight	200	200	200	200

Preparation method:

Tablets of Dexlansoprazole were prepared by direct compression method as per the formulae given in Table. All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine to a hardness of 6 kg/cm² using 8 mm concave punches.

EVALUATION STUDIES^{8,9,10}

a) Bulk Density

The powder was precisely weighed from all trials and was slightly shaken to breakdown any agglomerates formed. Then it was kept in the measuring cylinder of required quantity. The volume engaged by the granules was calculated. The bulk density of granules was calculated by the formula.

Bulk density = weight of sample taken /volume noted

b) Tap density

The granules were precisely weighed from all trials. It was slightly shaken to breakdown any agglomerates formed. Then it was kept in the measurable cylinder of required quantity. Then the measuring cylinder was tapped until there is no further variation in volume. This is the tapped volume. The tapped density of granules was calculated as given below.

Tapped density = weight of sample taken/tapped volume

Compressibility index

Carr's index also known as compressibility index is the index which determines the flow property with small quantity. Carr's indexes of the granules were calculated as given below,

Carr's index (%) = [(TBD-LBD)/ TBD] x100

Hausner's ratio

It is used to predict the flow property and this is underarticulate friction. Hausner's ratio was calculated as given below,

Hausner's Ratio = Tapped bulk density / Loose bulk density
The value of Hausner's ratio less than 1.25 directs good flow while higher than 1.5 directs poor flow.

Angle of repose

Angle of Repose It can be determined by using classic funnel method. The prepared granules which the flow property need to be analyzed was weighed accurately. The funnel height was accustomed in the way that the lowest just touched the top of heap of granules. Granules was permitted to freely flow through the funnel orifice to the surface. The radius of heap formed was measured. The angle of repose was determined using the equation.

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

Evaluation of tablet

Weight Variation

Weight variation is one of the official quality control tests for tablets. This is important because it directly relates with drug content. To do this test, minimum 20 tablets were weighed separately and average weight was calculated and compared with individual weight. The deviation gives the report of the weight variation. Usually, it is expressed in percentage. Weight variation should be done in process checking and for finished products.

Thickness

The dimensions like thickness and diameter of the tablets may have important effect in the drug content and other parameters. Hence it is required to maintain the thickness and diameter in the optimum acceptable range. This can be done by means of Vernier caliper. 10 tablets prepared from each trial were used. The average values were noted.

Tablet Hardness

Monsanto hardness tester was utilized to find the tablet hardness. In each formulation, 10 tablets were taken and the hardness was measured. The tablet was kept in the perfect position in the axis in the two jaws of instrument. The measurement should be zero kg/cm² at this stage. The knob is rotated to apply force to the tablet, the force is continued until there is fracture in the tablet. The point at which tablet breaks is break point and it was noted in kg/cm².

Friability

Tablet strength can be measured by using friabilator. This is performed to know the impact of shock abrasion on tablets when on travelling and handling. The test involves keeping the tablets in a plastic chamber and allowing it to revolve at 25rpm for 4 minutes that is equivalent to 100 rotations. In this test the tablets are subjected to drop at heights of 6 inches in each revolution. The initial weight and final weight of the tablets after dedusting were noted. The limit acceptable is less than 1% weight variation. It was calculated as follows. The percentage friability was measured using the formula,

$$\% F = \{1 - (W_o/W)\} \times 100$$

Drug Content

The drug content directly relates to the pharmacological efficacy, so it is mandatory to do the drug content test. It is an official quality control test. The drug content in all formulations were analyzed by triturating 20 tablets in mortar and pestle, then from the powder 75 mg equivalent of Dexlansoprazole was taken and transferred to 100ml standard volumetric flask. Then the volume was prepared to 50ml with pH 6.8 phosphate buffer. This was shaken for 15 min to mix. Then the volume was prepared to 100ml with phosphate buffer. The solution was strained by using whatmann filter paper and then it is diluted and absorbance was determined by using UV-Visible spectrophotometer at 255 nm using pH 6.8 phosphate buffer as blank.

In vitro release studies

This in vitro release can be done by using USP dissolution apparatus I. The test is performed at 50 rpm. The media used were pH 1.2 buffer for initial 2 h, followed by 8 h in pH 6.8 phosphate buffer. The temperature was maintained at 37 ± 0.5°C. The samples were taken at predetermined time and the dissolution basket is replenished with the buffer. The taken samples were filtered through filtered through a 0.45 membrane filter. The absorbance was measured at 255 nm.¹²

Stability studies:

The stability studies are performed to analyze the quality of drug and drug product with exposure to different temperature and humidity conditions on estimated time. General conditions like light, environment and other general parameters are maintained and the general evaluation tests were performed at different time interval periods. It is undesirable and time consuming to do full shelf-life period study. To avoid this accelerated stability studies has been adopted¹³.

3.RESULTS & DISCUSSION

FT-IR Spectrum of Dexlansoprazole

The compatibility between the drug and the selected excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymer and other chemicals.

SHIMADZU

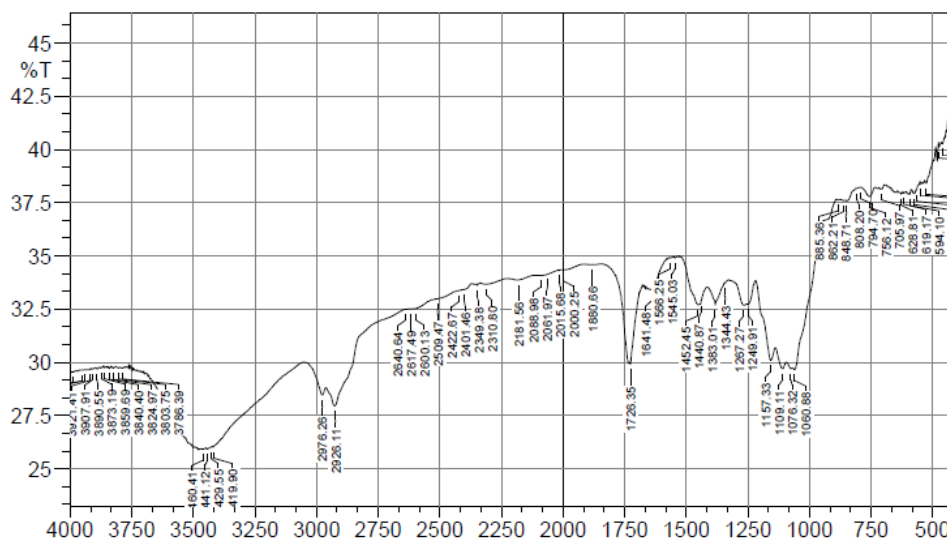


Fig-1: FTIR spectra of Dexlansoprazole

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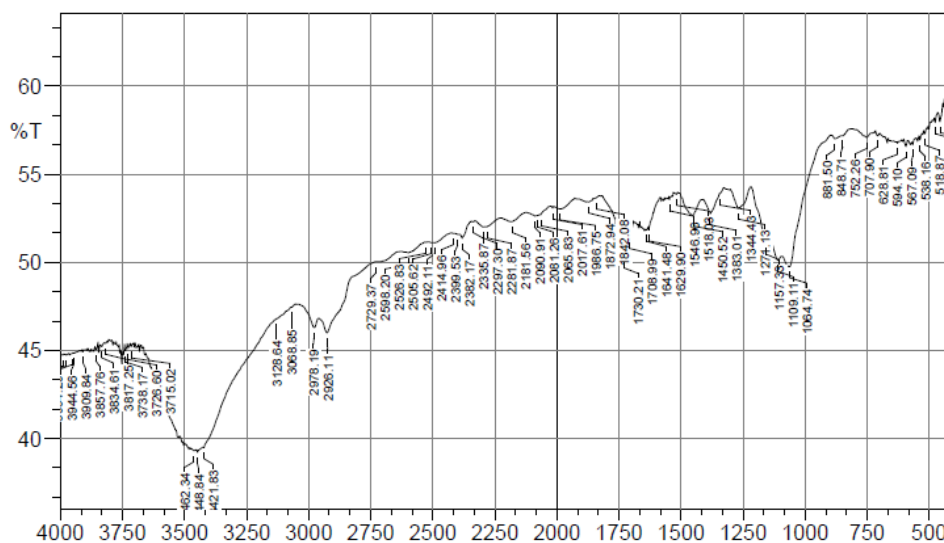


Fig-2: FTIR Spectra of physical mixture of drug and excipients

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits ($\pm 100 \text{ cm}^{-1}$) the drug is compatible with excipients.

EVALUATION STUDIES

Pre compression Parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.608-0.622.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.710-0.720.

Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27 to 30°

Compressibility index: Compressibility index was carried out, it found between 10% to 14.23 % indicating the powder blend have the required flow property for compression.

Table-2: Results of Pre compression parameters

F. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose (θ)
F1	0.620	0.710	13.15	1.14	28 ⁰
F2	0.612	0.718	14.23	1.17	29 ⁰
F3	0.622	0.719	13.46	1.14	30 ⁰
F4	0.619	0.720	13.89	1.17	255

Post compression parameters**Weight variation:**

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of $\pm 7.5\%$ of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 4.16 mm to 4.69 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 5.05 to 5.23 kg/cm². This ensures good handling characteristics of all batches.

Friability:

The % Friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F4 was found to be between 79.68 % and 83.67 % of Dexlansoprazole it complies with official specifications.

Table-3: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	100	4.16	5.12	0.40	79.68
F2	99	4.20	5.05	0.47	80.21
F3	100	4.17	5.19	0.55	83.67
F4	98	4.69	5.23	0.43	81.26

In-vitro Dissolution Study**Table-4: In vitro release data of tablet F₁ to F₄**

Time (hrs)	F ₁	F ₂	F ₃	F ₄
0	0	0	0	0
1	14.86	15.98	15.69	16.93
2	27.59	25.67	27.82	25.76
3	35.60	36.85	37.15	34.25
4	43.98	45.35	46.21	47.82
5	55.19	56.91	57.80	58.10
6	68.72	67.89	69.86	71.26
7	83.67	82.36	83.69	86.97
8	92.30	94.79	96.38	93.65

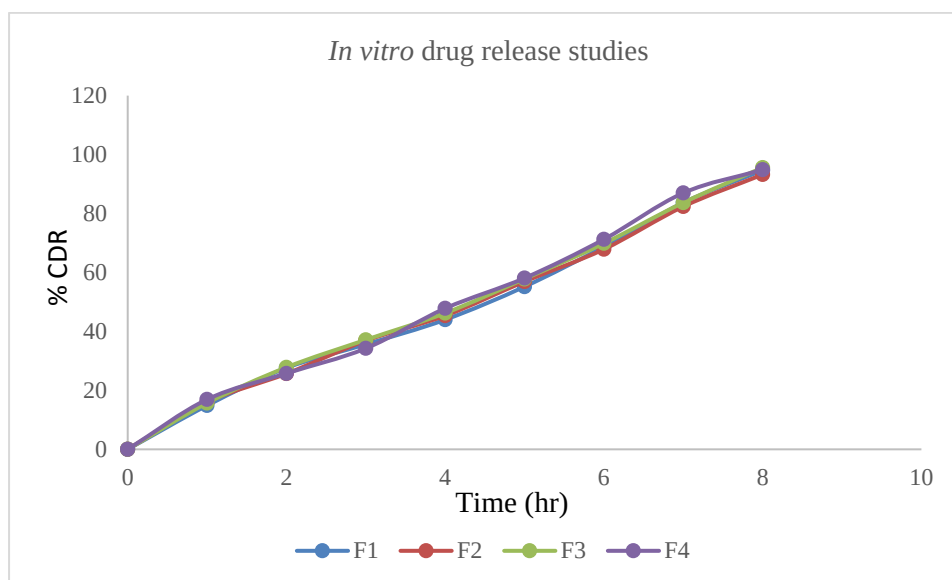


Fig-3: In vitro drug release studies of F1-F4 formulations

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 3 months.

Parameters quantified at various time intervals were shown;

Table-5: Results of stability studies of optimized formulation F3

Formulation Code	Parameters	Initial	1 st Month	2 nd	3 rd	Limits as per Specifications
F-3	25 ⁰ C/60%RH	96.38	95.76	94.71	93.30	Not less than
F-3	30 ⁰ C/75% RH	96.38	95.25	94.16	93.51	Not less than
F-3	40 ⁰ C/75% RH	96.38	95.06	94.38	93.10	Not less than

3.CONCLUSION

Oral route has been the predominantly adopted due to its convenience for drug delivery. This route is considered significantly in the pharmaceutical field, due to its flexibility in formulating the dosage form than other routes. This route of delivery depends on factors such delivery system type, the disease, the patient and the duration of therapy and the characteristic property of the drug. Almost all the oral controlled drug delivery systems follows diffusion or dissolution mechanism of drug release in the GIT.

In the present study, an effort was initiated to prepare the oral CR matrix tablets of Dexlansoprazole to provide a dosage form for prolonged period of time, in order to improve pharmacologic efficacy, reduce the total dose frequency and improved patient compliance. Infrared spectroscopy analysis established the absence of any drug polymer interaction. The CR matrix tablets were prepared by the direct compression method using different polymers as release retardant polymers. The powder was evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that granules showed excellent flow properties.

The resulting tablets were evaluated for official and unofficial tests like diameter, thickness, weight variation, hardness, friability and drug content. All the prepared tablet trials showed acceptable pharmacotechnical properties and passes the official pharmacopoeia standards. The in vitro release profiles were applied on various kinetic models. The release studies revealed that the release rate was decreased with increase in polymer proportion. From the results of present study, it appears that the release of Dexlansoprazole was significantly influenced by the characteristics of polymer and excipients used. In-vitro release from the formulation F3 with the hardness of 5.19 kg/cm². Higher hardness tablets contain a compact mass of polymer with relatively less pore, resulting in slower release. All other tested parameters of F3 formulation were in the acceptable limits. So formulation F3 was found to be better than other batch of formulations.

In the current research work, matrix formulation F3 containing Eudragit RS 100 were perhaps show maximum delay of drug release as optimum formulation among all formulations

Stability study was carried out with F3 formulation as per ICH guidelines and found to be stable both in accelerated and long-term stability conditions.

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