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FORMULATION AND EVALUATION OF DELAYED RELEASE DEXLANSOPRAZOLE TABLETS

Relli Usharani*, Ganta Pramodha

Department of Pharmaceutics, Nova College of pharmacy, Jupudi, Vijayawada, India.

ABSTRACT

Dexlansaprazole is a proton pump inhibitor, belongs to group of benzimidazole, used for the treatment of gastric and duodenum ulcers. Dexlansaprazole undergoes degradation in acid medium of the stomach, can be coated with enteric coating polymer that will safely deliver the drug in the small intestine. In this present study an attempt was made to formulate and evaluate Dexlansaprazole as enteric coated tablet. Delayed release tablets of Dexlansaprazole were prepared by wet granulation method using HPMC K4M and HPMC K15M, Avicel PH 102 (MCC) as filler and starch as binder. The prepared tablets were evaluated for hardness, weightvariation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, EudragitL100 by dip coating method. The *invitro* release was studied using pH 1.2 acidic buffer and pH6.8 phosphate buffer. The *in vitro* release study revealed that the prepared tablets were able to sustain release drug into the intestine. The release kinetics studies Showed that the release was zero order diffusion controlled and the nvalues obtained from the Korsmeyer-Peppas model showed that the release mechanism was supercase-II transport. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40°C/75 %RH for a period of 1month.

Key words: Dexlansaprazole, Delayed release, HPMC.

Author for correspondence:
Relli Usharani,
Department of Pharmaceutics,
Nova College of pharmacy,
Jupudi, Vijayawada, India

INTRODUCTION

A major causative factor (90%of gastric and 75% of duodenal ulcers) is chronic inflammation due to *Helicobacterpylori*, as piro chete that inhab it's the antral mucosa and increases gastric production. Gastric, in turn, stimulates the production of gastric acid by parietal cells. The gastric mucosa protects itself fromgastric acid with a layer of mucous, the secretion of which is stimulated by certain prostaglandins.Non-steroid anti-inflammatory drugs cyclooxygenase 1, which is essential for the production of these prostaglandins. Newer NSAIDs (celecoxib and rofecoxib) only inhibit cox-2, which is less essential in the gastric mucosa, and roughly halve the risk of non-steroid anti-inflammatory drugs (NSAID) relatedgastric ulceration. Glucocorticoids lead to atrophy of all epithelial tissues. Their role in ulcerogenesis is relatively small. Stress in the psychological sense has not been proven to influence the development of peptic ulcers. The goalin designing delayed or enteric coated delivery systemsis to improve the acid sensitive drugs and reduce the gastric irritation. If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would

be a single dose for duration of treatment, whether it is for days of weeks, as with infection, or for life time of the patient, as in hypertension or diabetes. Second, it should deliver the drug directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors orto localization to cells or to specific areas of the body. During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems.

Dr. Paul Ehrlich's'magic bullet'concept though realized late, offers a logical solutiontotheage-oldproblemofunrelatedandunwantedeffectsoftherap eutic agents and optimizing the drug therapy in its true sense. Although sustained/ controlled drug delivery can be considered as the progenitor of magic bullet concept in practice, the term sustained/controlled has been used with the widest possible meaning (1-4).

The primary treatment goals in patients with ulcer and gastro esophageal reflux disease rerelief of symptoms, prevention f complications related to the disease and healing of ulceration .Inhibition of the gastric proton pump is gaining acceptance as the treatment of choice for severe gastroesophageal reflux disease, and for treatment of duodenal and gastric ulceration. Dexlansoprazole is an oral delayed-release drug for the treatment of erosive esophagitis and gastro-oesophageal reflux disease for adult patients as well as patients aged 12-17. Enteric coated tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach [2] and release the drug in small intestine. Dexlansaprazole used to treat duodenal and gastric ulcers and it is also used for the treatment of gastric oesophageal reflux disease [3]. Its half life is around 1-2 hrs. For once in day administration. The delayed release tablet is intended to release the drug after some delay or after tablet pass GI Tract. Delayed release dosage form is best formulations which are used for drugs that are destroyed in gastric fluids or cause gastric Irritation, or are absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer & enteric coating layer [4] .The aim of proposed work was to formulate and characterize enteric coated tablets Dexlansaprazole for delayed release of drug in stomach for treatment of gastric and duodenal ulcers. Therefore, considering the importance of above said problems as well as the importance of treating ulcer,an attempt was made to formulate a delayed release tablet containing the anti-ulcer drug Dexlansaprazole.

MATERIALS AND METHODS (5-7)

Preparation of granules

Dexlansaprazole granules for tabletting were prepared by wet granulation method[42]. Specified quantity of Dexlansaprazole, hydroxypropyl methylcellulose (HPMC), and Avicel PH 102 were weighed according to the formula (Table-1) and transferred in a mortar and pestle and mixed thoroughly. The powder mass was mixed with 5% starchpaste to obtain as luggy mass and this was passed through sieve no12 to obtain the granules. The granules prepared were dried at 50^{o}C for4h. The dried granules were screened through sieve no 22 & 44 and stored for further studies. The specified quantity of magnesium stearate and talc were finally added and mixed for the compression of tablets.

Preparation of Dexlansaprazole tablets

An ideal mixture of granules were directly punched into tablets weighing about 200mg containing 60mg of Dexlansaprazole, using rotary tablet compression machine (12 stations, Karnavati, India), using 8 mm diameter concave punches. The different batches of Dexlansaprazole tablets were collected and stored in airtight containers.

Table-1 Formula for the preparation of Dexlansaprazole

Batch code	Dexlansaprazole (mg)	HPMC K4M	HPMC K15M	Avicel P	Starch paste	Talc (mg)	Magnesium stearate (mg)
F	30	20	-	144	qs	2	4
F	30	40	-	124	qs	2	4
F	30	60	-	104	qs	2	4
F	30	80	-	84	qs	2	4
F	30	100	-	64	qs	2	4
F	30	-	20	144	qs	2	4
F	30	-	40	124	qs	2	4
F	30	-	60	104	qs	2	4
F	30	-	80	84	qs	2	4
F	30	-	100	64	qs	2	4

***In vitro* drug release studies**

USP dissolution apparatus typeII was employed to study the *in vitro* drug release from various formulations prepared. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 10 h. The tablet was kept into the basket. The temperature was maintainedat37°C±0.5°Candthe stirring rate was

100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measuredbyUV-visible spectrophotometer at 260nm (pH1.2) and at 260nm (pH6.8) against a blank.The release studies were conducted in triplicate and the mean values were plotted versus time.

RESULTS AND DISCUSSION

Drugs Polymer Interaction Study by FTIR spectrophotometer

FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drug Dexlansaprazole and the polymers hydroxypropyl methylcellulose, Cassava starch, polyvinyl pyrrolidone used for the preparation of tablets. TheFT-IR was performed for drug, polymer and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies at wavelength between 4000 $cm^{-1}$to 400 cm^{-1} are given in Table-2.

Table-2 IR interpretation of drug, polymer and physical mixture of drug-polymer

SL. No	Interpretation	IR absorption bands (cm^{-1})		
		Pure drug	Drug + HPMC	Drug + HPMC K15M
1	N-H	3483.56	3487.42	3498.99
2	O-H	3358.18	3363.97	3248.23
3	CH_2	3176.87	3194.23	3196.15
4	CH_3	2960.83	2953.12	2939.61
5	C-O	1591.33	1591.33	1591.33
6	C-F	1373.36	1373.36	1377.22
7	S=O	1049.31	1039.67	1116.82

Post compression parameters

The Dexlansaprazole tablets were prepared by wet granulation method. The results of physicochemical evaluation of prepared tablets are shown in Table-3. The tablets were evaluated for Average weight, hardness, friability and drug content. The drug content was found to be between 94.57 ± 0.18% to 99.42±0.26%. The hardness was found to be from 4.73± 0.42 to 8.40 ± 0.002 kg/cm^{2}and in all the cases the friability was less than 1%.

Table-3 physicochemical evaluations of Dexlansaprazole tablets

Batch Code	Parameter			
	Hardness (kg/cm^2)	Friability (%)	Average weight (g)	Drug content (%)
F1	5.80 ± 0.12	0.012 ± 0.015	0.199 ± 0.12	97.71 ± 0.15
F2	6.20 ± 0.35	0.016 ± 0.025	0.204 ± 0.009	98.85 ± 0.34
F3	4.90 ± 0.21	0.005 ± 0.034	0.203 ± 0.024	97.42 ± 0.42
F4	4.93 ± 0.15	0.023 ± 0.015	0.208 ± 0.031	96.85 ± 0.16
F5	4.73 ± 0.42	0.024 ± 0.017	0.205 ± 0.015	97.14 ± 0.09
F6	8.06 ± 0.18	0.011 ± 0.034	0.198 ± 0.027	94.57 ± 0.18
F7	7.66 ± 0.09	0.019 ± 0.029	0.207 ± 0.034	95.42 ± 0.38
F8	5.56 ± 0.24	0.051 ± 0.017	0.206 ± 0.016	95.71 ± 0.27
F9	5.83 ± 0.08	0.032 ± 0.014	0.204 ± 0.006	95.71 ± 0.36
F10	6.21 ± 0.13	0.023 ± 0.013	0.199 ± 0.018	96.01 ± 0.15

***In vitro* drug release studies**

The *in vitro* dissolution studies were carried out for the prepared tablets using USP apparatus type II. The *invitro* release profiles of Dexlansaprazole tablets are shown in Figures 1-2. The cumulative percentage of release of Dexlansaprazole from the prepared tablets was varied from 65.02±0.42% to 99.26±0.16% depends upon the drug polymer ratio for 12 h.

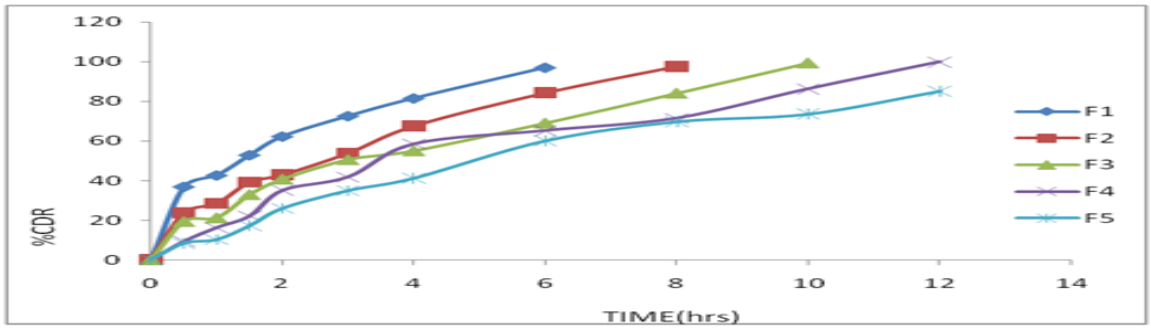

Fig-1 *in vitro* drug release studies of formulations F1-F5

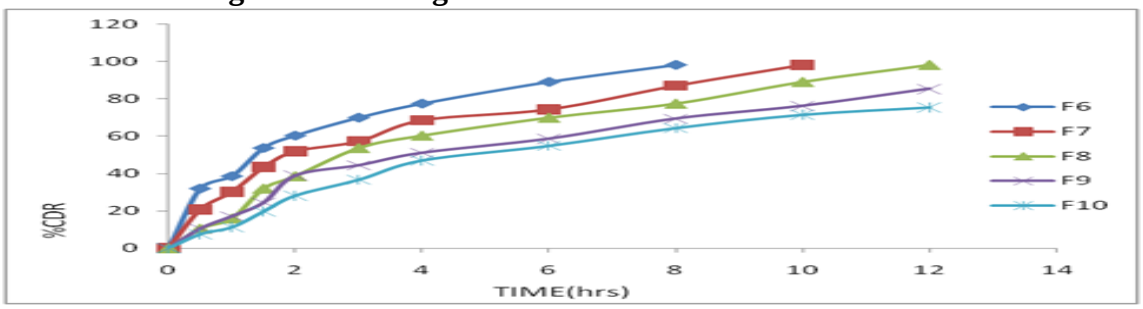

Fig-2 *in vitro* drug release studies of formulations F6-F10

***In vitro* drug release studies of enteric coated tablet**

Figures3 and 4 show the *in vitro* release profile of Dexlansaprazole from the various enteric coated tablets.

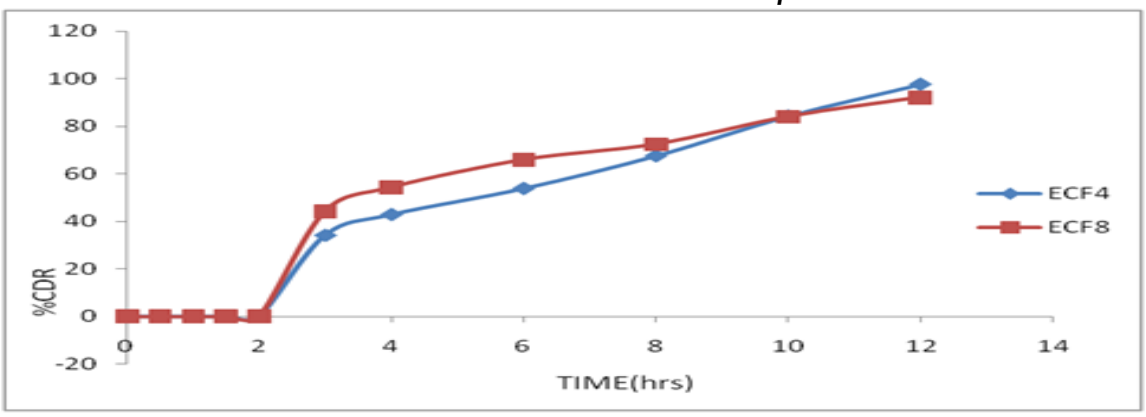

Fig-3 *Invitro* release of Dexlansaprazole from CAP coated ablet formulation ECF4 and ECF8

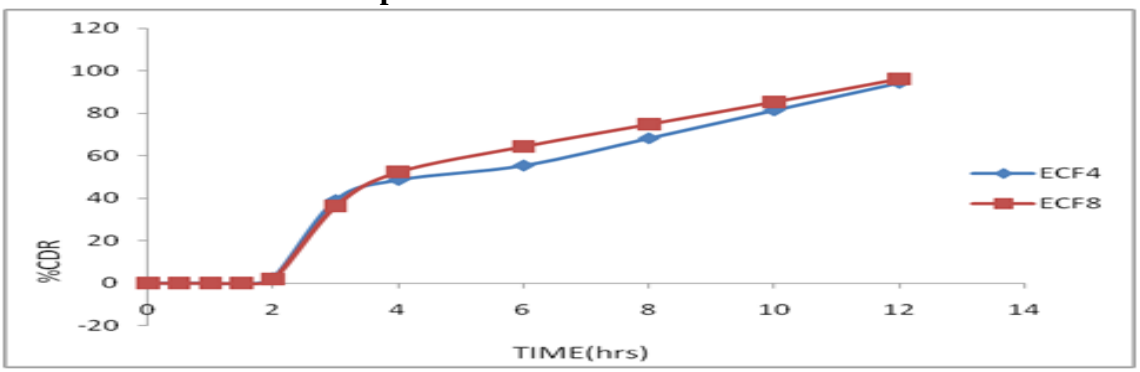

Fig-4 *Invitro* release of Dexlansaprazole from EudragitL100 coated tablet formulation ECF4 and ECF

CONCLUSION

Ulcers are crater-likes ores which form in the lining of the stomach, just below the stomach at the beginning of the small intestine in the duodenum. An ulcer is the results of fan imbalance between aggressive and defensive factors. Dexlansoprazole is a proton pump inhibitor and R-enantiomer of lansoprazole. Its dual-delivery system is intended for extended plasma concentration and therapeutic effects, in comparison to other single-release proton pump inhibitors. The stability of Dexlansaprazole is a function of pH and it rapidly degrades in acid medium of the stomach, but has acceptable stability in alkaline conditions. Therefore, Dexlansaprazole should be delivered into the intestine. Hence, an attempt was made to formulate a delayed release drug delivery system for Dexlansaprazole by using various enteric coating polymers. The main objective of the study was to developed layed release tablets of Dexlansaprazole. The study led the following conclusions: The drug Dexlansaprazole was selected for the study, because of its availability, proved activity and better clinical applications. The compatibility studies usingFT-IR revealed that there was no interaction between the selected drug Dexlansaprazole and the polymers HPMC. The Dexlansaprazole granules were prepared by wet granulation method. The physicochemical parameters of the granules observed support the ideal flow nature of the formulated granules. The Dexlansaprazole tablets were prepared by wetgranulation method. The physicochemical evaluation of the prepared tablets was found within the standards Pharmacopeial limits. The selected formulations ECF4, ECF8 were subjected torelease kinetics, stability studies. The drug release from the optimized formulation (ECF4) was zero order and release mechanism was supercase-transport. The stability study indicated that the prepared formulation was stable and retained their pharmaceutical properties at room temperature and 40°C/75% RH over a period of 1 month. The cellulose acetate phthalate coated tablets did not release the drug in hostile acidic environment (pH 1.2) due to protective polymer coating and released the drug in the intestinal environment (pH 6.8).

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