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FORMULATION AND EVALUATION OF MODIFIED RELEASE TABLETS OF DEXLANSOPRAZOLE

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Abstract:The current research work has been aimed at designing controlled release tablets dosage form for Dexlansoprazole. Dexlansoprazole is a Proton Pump Inhibitors (PPI), used in the treatment of Gastroesophageal reflux disease (GERD). Controlled release drug delivery systems offers improved patient compliance, better therapeutic efficacy, lesser side effects and reduced dosage regimen. Dexlansoprazole having short biological half life, therefore it is considered as an appropriate drug for the composition of controlled release tablets to prolong its therapeutic action. Controlled release tablets of both the drugs were formulated by Direct compression technique, by contradictory polymers akin to different grades polymer such as Carbopol-974P, Hydroxypropyl methyl cellulose (HPMC) grades of HPMC-K4M, HPMC-K15M, HPMC-K100M, Sodium Carboxy Methyl Cellulose. Dexlansoprazole prepared compositions were subjected to evaluate for the pre compression parameters for instance bulk density, tapped density, hausner's ratio, carr's index, angle of repose and post compression parameters such as thickness, weight variation, hardness, friability, drug content. All the formulations met predefined stipulation.The *in-vitro* drug dissolution optimized CR tablet dosage containing Drug to Polymer (Dexlansoprazole: Carbopol-974P: HPMC K4M) at 1:1.5:1.5 ratios (F-2) has shown the cumulative % drug dissolved of 98.79% at the end of 24 hrs. The formulation which has shown the drug release at Zero order / persistently for the preferred time period of time was considered as both the optimized formulation. Based on *in-vitro* drug dissolution profiles, it was evidently that the cumulative % drug release from Dexlansoprazole optimized CR tablet dosage form has been controlled for 24 hrs.
Keywords: Dexlansoprazole, Gastroesophageal reflux disease, Hydroxypropyl methyl cellulose, in-vitro drug dissolution.

I. INTRODUCTION: Most conventional oral drug products, such as tablets and capsules are formulated to release the active drug immediately after oral administration, to acquire quick and entire systemic drug absorption, such immediate release products result in comparatively rapid drug absorption and onset of associated pharmacodynamic effects. Although, after absorption of the drug from the dosage form is whole, plasma drug concentrations refuse according to the drug's PK profile. Ultimately plasma drug concentrations reduce below the minimum effective plasma concentration (MEC), ensuing in loss of therapeutic activity. Before this point is reached, another dose is frequently given if a sustained therapeutic effect is required. A substitute to administer an additional dose is to use a dosage form that will afford sustained drug release, and hence maintain plasma drug concentrations, ahead of what is typically seen using immediate release dosage forms[1]. A modified- release dosage form is defined "as one for which the drug release characteristics of time course and/or location are preferred to achieve therapeutic or convenience objectives not accessible by conventional dosage forms such as solutions, ointments, or punctually dissolving dosage forms as presently recognized". Modified release drug products are considered for altered routes of administration based on the physico chemical, pharmacologic and PK properties of the drug and on the properties of the materials used in the dosage form. Numerous unlike terms are now defined to describe the available types of modified release drug products based on the drug release characteristics of the products[2].

Types of Oral Controlled Release Drug Delivery Systems[3,4]:

A number of techniques are used to achieve controlled release of drugs via the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems.
- Diffusion controlled release systems.
- Diffusion and dissolution systems.
- Osmotically controlled release systems.

- Gastro retentive drug delivery systems.
- Electrically stimulated release devices.
- Ion-exchange resins.

Mechanism of Action[5]: Dexlansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H, K)- ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (-proton) pump within the parietal cell, Dexlansoprazole has been characterized as a gastric proton- pump inhibitor, in that it blocks the final step of acid production.

II. MATERIALS AND METHODS:

A gift sample of Dexlansoprazole was obtained from ZIM Laboratories, Nagpur, Carbopol-974P, Aerosil were obtained by Yarrow Chem. Products, Mumbai, HPMC from Otto Chemie Pvt. Ltd, Mumbai, were obtained by Akhil Health care Pvt. Ltd, Gujarat and all other chemicals & reagents were of SD fine chemicals provided by the college.

Preparation of Tablets by Direct Compression method[6,7,8,9]:

Different tablets formulations were prepared by direct compression technique. All powders were passed through 60mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests.

Table 1: Compositions of Dexlansoprazole CR tablets with HPMC

Ingredients(mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Dexlansoprazole	30	30	30	30	30	30	30	30	30	30	30	30
Carbopol-974 P	100	75	50	100	75	50	100	75	50	---	---	---
HPMC K4M	50	75	100	---	---	---	---	---	---	---	---	---
HPMC K 15M	---	---	---	50	75	100	---	---	---	75	50	100
HPMC K 100M	---	---	---	---	---	---	50	75	100	---	---	---
Sodium CMC	---	---	---	---	---	---	---	---	---	75	100	50
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
MCC	60	60	60	60	60	60	60	60	60	60	60	60
Total weight (mg)	250	250	250	250	250	250	250	250	250	250	250	250

III. RESULTS & DISCUSSION:

Pre Formulation Studies:

Tablet powder blend was subjected to various preformulation parameters. The bulk density of all the formulations was found to be in the range of 0.34±0.06 to 0.49±0.05 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.51±0.02 to 0.77±0.01 showing the powder has good flow properties. The hausner's ratio ranging between 0.9±0.29 to 1.15±0.24 indicating the powder has good flow properties. The Carr's index of all the formulations was found to be in the range of 11.68±0.07 to 16.36±0.34. The angle of repose of all the formulations was found to be in the range of 25°.1'±0.30 to 30°.3'±0.65. All these value indicates that the powder blend has good flow properties.

Table 2: Precompressional Properties of all the formulation

Formulation Code	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner ratio (HR)	Carr's index (CI)	Angle of repose (θ)
F1	0.36±0.09	0.69±0.06	1.2±0.09	12.18±0.97	25°.6'±0.18
F2	0.35±0.09	0.61±0.07	1.1±0.26	13.63±0.86	25°.1'±0.30
F3	0.47±0.07	0.74±0.05	1.13±0.01	13.55±0.43	26°.2'±0.42
F4	0.34±0.06	0.55±0.07	0.9±0.36	12.26±0.31	30°.3'±0.65
F5	0.42±0.04	0.51±0.02	0.9±0.29	11.68±0.07	26°.9'±1.12
F6	0.49±0.05	0.64±0.09	0.97±0.17	16.36±0.34	29°.7'±0.79
F7	0.43±0.05	0.77±0.01	1.1±0.58	14.36±0.98	27°.2'±0.65
F8	0.40±0.07	0.60±0.09	1.11±0.32	12.75±0.46	25°.3'±0.98
F9	0.46±0.08	0.61±0.04	1.15±0.24	11.87±0.76	28°.6'±0.54
F10	0.39±0.06	0.52±0.05	0.7±0.76	14.87±0.53	28°.7'±1.20
F11	0.46±0.03	0.64±0.07	1.14±0.53	14.63±0.75	29°.9'±0.27
F12	0.38±0.02	0.63±0.04	0.9±0.66	12.55±0.59	26°.5'±0.24

Post Compression parameters:

Weight Variation:

Tablets of each batch were subjected to weight variation test,difference in weight and percent deviation was calculated for each tablet. Average weight of the tablet is approximately in range of 248±0.75 to 251.6±0.86, so the permissible limit is ± 5% (more than 250mg). The tablet weights were within the Pharmacopoeial specifications.

Tablet Hardness:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester. The results showed that the hardness of tablets was found to be in the range of 3.6±0.34 to 4.9±0.89kg/cm^2. This indicates good tablet strength.

Percent Friability:

Percentage friability of all the formulations was found to be in between 0.55±0.53 to 0.79±0.04%. This indicated good handling property of the prepared CR tablet.

Diameter and Thickness:

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. The size (diameter) of the tablets of all formulations were found to be 8.0±0.0 mm and thickness ranged between 3.24±0.53 to 4.1±0.07.

Drug content:

The content of active ingredients in the formulation was found to be between 98.13±0.02 to 101.2±0.07%w/w, which is within the specified limit as per IP (i.e. 90-110% w/w).

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 3: Post compressional Properties of all the formulation

Formulation Code	Weight variation(mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)	Drug content (%)
F1	249±0.23	3.9±0.72	0.58±0.42	3.25±0.97	99.41±0.26
F2	250±0.67	4.9±0.89	0.59±0.53	3.98±0.71	99.98±0.03
F3	251±0.75	3.9±0.46	0.62±0.61	3.69±0.23	101.2±0.07
F4	250±0.55	4.3±0.63	0.59±0.17	3.59±0.62	99.26±0.09
F5	249±0.05	4.3±0.18	0.79±0.15	4.1±0.07	99.24±0.75
F6	251±0.86	4.1±0.52	0.62±0.55	3.24±0.53	101±0.12
F7	249±0.98	3.9±0.14	0.55±0.53	3.66±0.35	99.3±0.87
F8	251±0.65	3.6±0.34	0.61±0.43	3.37±0.79	100±0.98
F9	250±0.95	4.1±0.53	0.71±0.65	4.3±0.64	99.8±0.42
F10	249±0.03	3.9±0.79	0.69±0.82	3.27±0.67	99.2±0.01
F11	248±0.75	4.4±0.62	0.65±0.16	3.52±0.16	98.13±0.02
F12	249±0.52	4.1±0.14	0.79±0.04	3.78±0.97	99.3±0.17

***IN-VITRO* DRUG RELEASE STUDIES**

The results of drug release shown that the Dexlansoprazole was released in a controlled behaviour in all the formulations whereas formulation F-2 showed maximum cumulative % drug release i.e. 98.79±0.48 at the end of 24 hours which was the intent of the finalized formulation (to prolong the drug release up to 24 hrs) while others being not reached to the time point of maximum release still extending the release

Table 4: Invitro drug release data of formulation F1-F6

Time in hrs	Cumulative % drug released					
	F1	F2	F3	F4	F5	F6
1	19.13±0.82	6.23±0.86	10.45±0.61	21.76±0.78	16.76±0.68	17.49±0.75
2	35.64±0.33	9.64±0.51	19.59±0.29	38.46±1.06	24.43±0.74	36.38±0.43
4	47.56±0.38	27.13±0.86	25.11±0.48	41.03±1.08	38.96±0.98	42.76±0.34
6	59.43±0.92	39.80±0.11	29.67±0.14	53.49±0.98	51.29±1.02	58.96±0.28
8	69.49±0.46	48.18±0.18	37.53±0.12	57.84±0.84	58.46±0.84	61.22±0.56
10	84.63±0.36	55.17±0.13	54.22±0.18	61.98±0.68	63.86±0.98	64.76±0.98
12	88.68±0.63	63.36±0.65	66.53±0.27	70.72±0.73	69.16±0.48	69.23±0.84
14	96.75±0.79	71.24±0.69	72.3±0.44	74.39±0.25	74.69±0.68	71.46±0.67
16	99.57±0.35	79.92±0.31	83.41±0.48	78.67±0.43	75.46±0.84	73.34±0.68
18	-----	86.18±0.77	85.96±0.89	83.38±0.57	79.47±0.56	74.31±0.84
20	-----	90.17±0.14	87.43±0.11	85.64±0.48	82.46±0.76	76.69±0.76
22	-----	95.86±0.22	88.39±0.18	88.46±0.74	84.76±0.84	78.46±0.48
24	-----	98.79±0.48	90.31±0.74	91.23±0.66	86.16±0.67	80.23±0.78

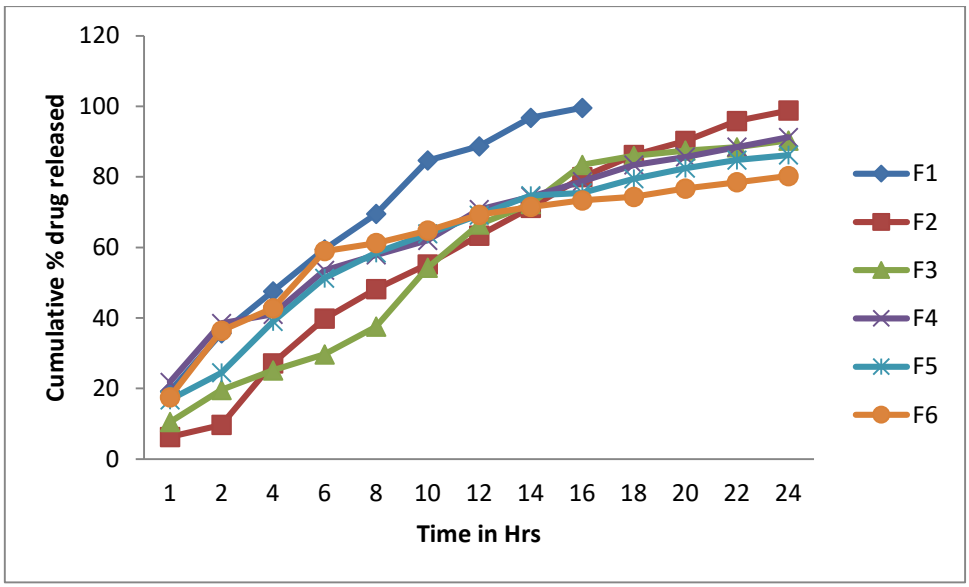

Fig 1: Invitro drug release curve of formulation F1-F6

Table 5: Invitro drug release of formulation F7-F12

Time in Hrs	Cumulative % drug released					
	F7	F8	F9	F10	F11	F12
1	12.34±0.87	15.12±0.65	6.35±0.41	23.88±0.94	17.82±0.35	9.57±0.84
2	17.53±0.54	28.35±0.44	15.74±0.26	49.32±1.32	18.9±0.48	22.68±0.72
4	26.89±0.35	37.54±0.76	22.83±0.34	53.92±0.84	31.13±0.78	26.1±0.98
6	38.67±0.86	49.76±0.82	30.55±0.98	63.07±0.67	60.84±1.01	28.09±1.04
8	47.52±0.56	51.14±0.59	38.75±0.65	71.77±1.24	75.6±1.28	55.8±1.32
10	56.89±0.87	59.98±0.34	45.97±0.76	77.85±0.98	84.49±0.37	69.3±0.37
12	65.53±0.34	62.15±0.98	53.42±0.45	83.76±1.09	92.7±0.68	76.5±0.67
14	70.98±0.65	67.45±0.39	61.76±0.78	86.34±0.98	93.18±1.38	80.45±0.32
16	76.57±0.89	74.68±0.62	67.41±0.57	89.43±0.65	94.08±0.84	83.1±0.84
18	80.65±0.45	79.25±0.45	74.43±0.34	93.6±1.24	94.59±1.24	83.6±0.47
20	84.25±0.32	80.87±0.85	81.76±0.32	93.67±1.42	95±0.84	84.6±1.24
22	86.73±0.76	84.54±0.56	88.98±0.87	95.86±0.67	95.67±0.69	85.09±0.86
24	89.36±0.45	87.35±0.37	93.56±0.54	96.9±0.82	96.24±0.84	85.79±0.78

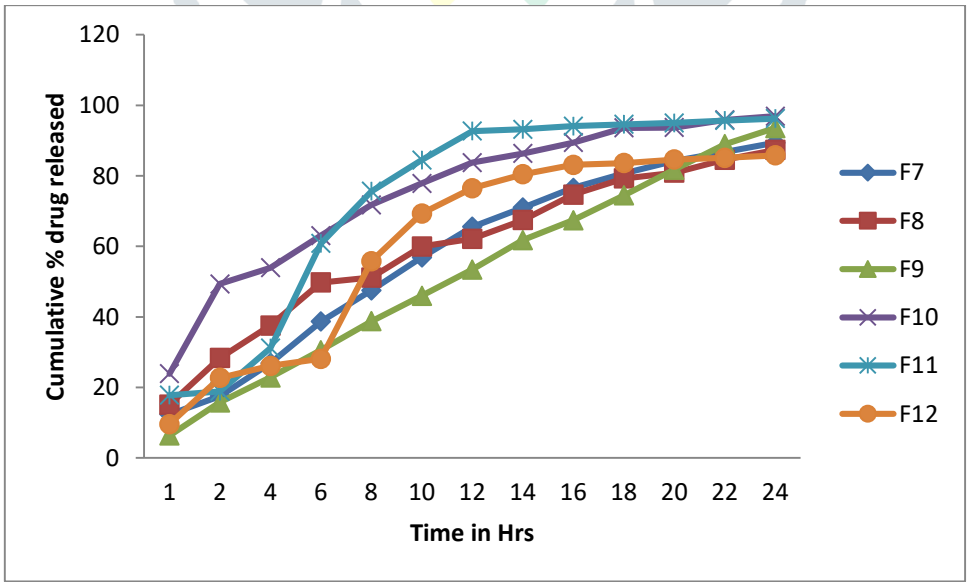

Fig 2: Invitro drug release curve of formulation F7-F12

Cumulative Drug Release at t50 % and t90 % :

The cumulative drug release of Formulation F1 to F12 where t50 is time at which 50% drug was released and t90 is time at which 90% drug is released.

Table 6: Drug Release of t50% and t90%

Formulation code	t50 (%) hrs	t90 (%) hrs
F1	4.38	12.33
F2	8.33	19.52
F3	9.31	23.45
F4	5.41	23.32
F5	5.48	---
F6	5.10	---
F7	8.55	---
F8	7.16	----
F9	11.21	22.13
F10	2.37	16.55
F11	5.05	11.35
F12	7.42	---

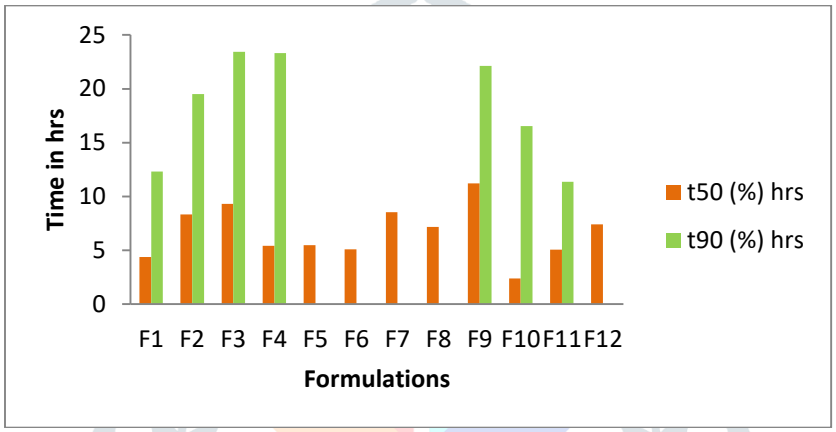

Fig 3: Bar graph of Drug Release of t50% and t90%

IV. CONCLUSION:

From the above study it was concluded that the developing the dexlansoprazole controlled release tablet is possible and it can be an crucial development in curing the Gastroesophageal reflux disease (GERD) and Ulcerative colites by decreasing the dose frequency increasing bio-availability and also reducing the dose dumping which might help in curing the disease effectively.

All the formulations met predefined stipulation.The *in-vitro* drug dissolution optimized CR tablet dosage containing Drug to Polymer (Dexlansoprazole: Carbopol- 974P: HPMC K4M) at 1:1.5:1.5 ratios (F-2) has shown the cumulative % drug dissolved of 98.79% at the end of 24 hrs.

The formulation which has shown the drug release at Zero order / persistently for the preferred time period of time was considered as both the optimized formulation. Based on *in-vitro* drug dissolution profiles, it was evidently that the cumulative % drug release from Dexlansoprazole optimized CR tablet dosage form has been controlled for 24 hrs.

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