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Formulation and Preparation of Mucoadhesive Drug Delivery System of Benzimidazole Class Proton Pump Inhibitors in Gastroesophageal Reflux Disease

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ABSTRACT: *The main objective of the study was to develop an uncoated transmucosal quick-dissolving medication delivery system for gastroesophageal reflux disease using wet granulation method. The formulation of transmucosal benzimidazole tablets without a coating was the goal. Since enteric-coated benzimidazole tablets often dissolve in the gastrointestinal canal below the stomach after passing through the stomach unscathed, the first step in the manufacturing process left the tablets without coating. As a result, the action started later than expected. Technology for uncoated transmucosal drug delivery was created to overcome the drawback of enteric-coated PPIs of the benzimidazole class tablets.*
The ability of a dosage form to carry active substances to the site of action in an amount sufficient to produce the desired pharmacological response is its most crucial characteristic. Establishing an uncoated transmucosal fast-dissolving medication delivery system for the treatment of GERD disease was the aim of the study. This dosage form was predicted to accelerate the rate of dissolution, absorb the oral transmucosal dosage form in the oral cavity, accelerate the commencement of action, enhance therapeutic efficacy, and raise medication safety.
The following steps were taken in the research to design and assess transmucosal fast dissolving tablets of benzimidazole using the wet granulation process with excipients such as crospovidone, lactose monohydrate, sodium starch glycolate, sodium steryl fumarate, and silica.
Keywords: *Mucoadhesion, mucoadhesive drug delivery systems, Evaluation methods, PPI, GERD.*

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I. INTRODUCTION

A disorder known as gastroesophageal reflux disease (GERD) occurs when food or liquid from the stomach leaks backward into the oesophagus, which is the tube that connects the mouth to the stomach. Heartburn and other symptoms may result from this activity irritating the oesophagus [1].

1.1 Causes, incidence, and risk factors:

When you eat, food passes down the oesophagus, also known as the food pipe or swallowing tube, from the throat to the stomach. A ring of muscle fibres keeps food from going backward into the oesophagus once it has entered the stomach. The lower esophageal sphincter, or LES, is the name given to these muscular fibres. Food, drink, and stomach acid can flow back into the oesophagus if this sphincter muscle does not seal tightly. Reflux or gastroesophageal reflux is the term used for this. Reflux can harm the oesophagus or just create symptoms [2].

1.2 The risk factors for reflux include:

- Alcohol (possibly)
- Hiatal hernia (a condition in which part of the stomach moves above the diaphragm,which is the muscle that separates the chest and abdominal cavities) [3]
- Obesity
- Pregnancy
- Scleroderma
- Smoking

1.3 **Symptoms:**

More common symptoms are:

- Feeling that food is stuck behind the breastbone
- burning pain in the chest (under the breastbone)
- Increased by bending, stooping, lying down, or eating
- More likely or worse at night
- Relieved by antacids
- Nausea after eating

1.4 **Diagnostic strategies:**

1.4.1 Trial of treatment-

Typical symptoms like heartburn or regurgitation in the clinical history are typically used to make a diagnosis. When a patient's medical history suggests they may have uncomplicated GERD, a 2-week trial of treatment with a proton pump inhibitor (PPI) is advised since it offers the quickest and most affordable means of confirming the diagnosis. Positive response to PPI therapy is at least as sensitive and precise as 24-hour intraesophageal pH monitoring, which is still frequently regarded as the "gold standard" for the diagnosis of GERD in patients with symptoms suggestive of the condition. Additionally, a patient's complete lack of improvement in response to PPI therapy strongly suggests that they do not have GERD, necessitating additional testing and perhaps a reconsideration of the original diagnosis [4]. Below is a chart that illustrates the therapy study.

1.4.2 Current medical therapy for GERD:

To lessen the corrosive and irritating effects of the refluxant, drugs that lower gastric acidity have been utilised as first-line treatments for GERD. H2RAs, which are powerful inhibitors of gastric acid release and can significantly lower the need for surgery for patients with peptic ulcers and gastroduodenal ulcers, are histamine H2- receptor antagonists.

When used to treat GERD patients, H2RAs have three significant drawbacks. First off, most individuals with gastro-esophageal reflux experience it during the daytime postprandial period, and their acid-suppressing effects are reduced during this time compared to the nighttime period. Second, H2RAs' acid-suppressing actions become more pronounced after 2 weeks of daily continuous dosing. Third, because H2RAs are primarily excreted through the kidneys, the dose of these drugs must be modified based on renal function [5].

1.4.3. Proton-pump inhibitors (PPI's):

Proton pump inhibitors (PPIs), which prevent the production of gastric acid regardless of the initial stimulus, are used to treat GERD symptoms such heartburn and other gastrointestinal symptoms as well as gastric and duodenal ulcerative diseases [6].

1.4.3.1 Mechanism of action:

The H+/K+ adenosine triphosphate (also known as acid pump or proton pump) enzyme, which is in the gastric parietal cells, is the primary mechanism of action of PPIs. These drugs are converted in the parietal cells to active sulfonamide metabolites, which disable the proton pump's sulfhydryl group and lessen hydrogen ion secretion [7].

1.4.3.2. PPi's used in research:

- There are several different molecules in the class, one of which is an isomer.
- Both local and large global businesses market the substances in the class.
- The class has a significant market value of about R320 million, and the producers effectively defend their market share through advertising and marketing. [8]
- During the study's time frame, many generics were introduced to the market.
- In the class, therapeutic and generic substitution is common.

II. MATERIALSAND METHODS

2.1 MATERIALS: -

The benzaimidazole sesquihydrate had been acquired from Sun Pharma in Badodara. These two polymers were used: eudragit L 100-55 from Rohm Pharma in Darmstadt, Germany, and sodium alginate from Loba Chemi Pvt. Ltd. in Mumbai.All other substances were graded as analytical.

2.2 METHODS: -

2.2.1 Identification of pure drug

FT-IR analysis was used to examine and compare the identification of Benzaimidazole ole to the reference drug spectra.

2.2.2 Method used to estimate Benzaimidazole

10 g/ml solutions of the drug Benzaimidazole were created by dissolving it in phosphate buffer 6.8. In a double beam UV-VIS Spectrophotometer, the same was further diluted, and the maximum absorbance (max) was measured between a U.V range of 200 to 400 nm against phosphate buffer pH 7.2 as a blank. The maximum absorbance (max) was discovered to be 292 nm.

2.2.3. Preparation of Benzaimidazole tablet

All the excipients were sieved through a #60BSS sieve, except for benzimidazole, magnesium stearate, and colloidal anhydrous silica. After passing through a #40BSS filter, benzoimidazole was combined with the step 1 excipients. The mixture from step 2 was ground up using water, and the resulting granules were filtered through a #22 BSS sieve and dried in trays at 40°C. Magnesium stearate was used to lubricate the dry granules after which silica was filtered through a #60BSS sieve. A 6 mm circular tool was used to crush the lubricated granules.

Table 2.1 Composition of batches

S. No.	Ingredients(mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	API	30	30	30	30	30	30	30
2	MCC	-	-	40	40	15	15	15
3	Lactose Monohydrate	30	30	-	-	15	15	15
4	Starch	7	7	-	-	-	-	-
5	SSG	5	-	-	5	6	-	2
6	Crospovidone	-	5	5	-	-	6	2
7	Sodium bicarbonate	3	3	3	3	3	3	3
8	Magnesiumcarbonate	15	15	15	15	15	15	15
9	Mannitol	6.5	6.5	3.5	3.5	12.5	12.5	14.5
10	Aspartame	3	3	3	3	3	3	3
11	Magnesiumstearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25
12	Silica	0.25	0.25	0.25	0.25	0.25	0.25	0.25
	Total	100	100	100	100	100	100	100

Qs= quantity sufficient

III. STUDY OF DIFFERENT PARAMETERS

3.1 Drug content uniformity

Each batch's ten randomly chosen tablets were weighed and ground into powder using a pestle and mortar. In a 100 ml volumetric flask, 30 mg of the drug's powder was transferred and dissolved for 15 minutes in around 40 ml of distilled water. Through PVDF filter paper, the fluid was filtered. Water was used to clean the filter paper. The washing was combined with the filtrate to create a final volume of 100 ml. The absorbance was measured at 292 nm against the blank after the proper dilution. The details on the drug content are shown in table 4.3.

3.2 In-vitro release studies

The designed formulations' in-vitro dissolution profile was tested using USP type I equipment under the predetermined circumstances (Temp 37 0.5oC, 100 rpm). The samples were spectrophotometrically examined at 292 nm for the presence of drugs in comparison to the corresponding buffer blank. From a typical graph, the average proportion of benzoimidazole released at different time points was determined and plotted against time.

IV. RESULTS & DISCUSSION

4.1 Compatibility studies

Studies using FT-IR were conducted. The drug was determined to be either pure or not, and the FT-IR data demonstrated that there is no interaction between the drug and excipients.

The maximum wavelength of the benzimidazole absorption spectrum (max.) in several mediums (distilled water, 0.1 N HCl, and phosphate buffer 6.8) was discovered to be at 292 nm. A systronic UV-2202 spectrophotometer was used to evaluate the absorbance of each produced solution of benzimidazole in various mediums at 292 nm in comparison to pure water, 0.1 N HCl, and phosphate buffer 6.8 as a blank.

4.2 Evaluation of pre-compression parameters

Wet granulation was used to create the drugs and excipient combination. The results are provided in Table 4.1. The granules were assessed for percentage yield, granule particle size, angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index. The yield as a percentage ranged from 91.68 to 97.82%. The granules' particle sizes ranged from 0.498 0.05 mm to 0.548 0.11 mm. The granules' bulk densities were discovered to be between 0.468 0.03 to 0.521 0.04 gm/ml. The range of the angle of repose was 25.79 0.24 to 28.27 0.34. The densities that were tapped ranged from 0.540 0.04 to 0.596 0.05 gm/ml. Hausner's ratio was ranged between 1.132 ± 0.02 to 1.154± 0.07, while the compressibility index was in the range of 12.48 ± 0.12 to 15.42 ± 0.20.

4.3 EVALUATION OF POST- COMPRESSION PARAMETERS

By using the wet granulation method, seven batches of compressed formulated tablets of benzimidazole with excipients were characterised for weight uniformity (passed), drug content (98.760.4 to 99.50.03), hardness (3.2 to 4.7 kg/cm2), friability (0.11 to 0.25%), wetting time 54sec to 32, water absorption ratio 12.31 to 18.48, and disintegration time (241 to 21 sec). The F7 batch had the fastest disintegration because it contained crospovidone and sodium starch glycolate, which allowed water to be absorbed from capillary action in the best possible way. As a result, the F7 batch's disintegration time was significantly shorter. The type of super disintegrants we employ affects how wettable our pills are.

Table. 4.1 Physicochemical evaluations of benzimidazole granules

Formulation	Bulk density(gm/cm^2)	Tapped density(gm/cm^2)	Carr's Index (%)	Hausner' ratio (HR)	Angle of repose(ɵ)
F1	0.514±0.002	0.588±0.003	12.58±2.54	1.143±0.05	25°
F2	0.504±0.004	0.582 ±0.002	15.47±3.14	1.154±0.03	26°
F3	0.468±0.001	0.540±0.003	13.3±2.15	1.153±0.05	28°
F4	0.506±0.005	0.584±0.003	15.42±1.31	1.151±0.07	26°
F5	0.516±0.002	0.590±0.001	12.60±2.15	1.132±0.04	25°
F6	0.521±0.002	0.596±0.001	12.59±2.26	1.144±0.03	24°
F7	0.498±0.004	0.569±0.003	12.48±2.14	1.142±0.04	25°

(n=3 ± S.D)

Table 4.2 Physicochemical evaluations of benzimidazole tablets

Batches	Avg. Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	FB (%)	DT (sec.)	Wetting Time (sec.)	WaterAbs. ratio
F1	100.67	98.76±0.02	3.2±0.09	0.21±0.14	242±1.5	54±2.6	16.71
F2	99.87	99.83±0.02	4.5±0.11	0.15±0.11	211±3.5	51±2	13.35
F3	100.33	99.20±0.11	4.7±0.14	0.14±0.09	34±2.5	44±3	20.87
F4	98.76	97.56±0.05	3.6±0.11	0.24±0.06	33±3.7	39±3.5	12.31
F5	99.89	97.62±0.11	2.9±0.11	0.11±0.13	29±2.7	37±3.5	13.35
F6	100.01	98.92±0.01	3.9±0.14	0.25±0.09	29±2.5	39±2.5	15.30
F7	100.23	99.55±0.03	4.7±0.16	0.22±0.13	21±2	32±3.5	16.21

* (n=5 ± S.D) ** (n=2 ± S.D) *** (n=3 ± S.D)

Table.4.3. In-vitro drug release of formulations F1-F7

Time (min.)	% Drug released						
	F1	F2	F3	F4	F5	F6	F7
5	38.44 ± O.25	45.12 ± 0.21	54.81 ± 0.21	54.47 ± 0.45	55.14 ± 0.25	56.22 ± 0.35	56.14 ± 0.25
10	44.87 ± 0.59	55.50 ± 0.40	61.81 ± 0.17	65.50 ± 0.51	64.15 ± 0.35	66.15 ± 0.35	65.48 ± 0.40
15	51.89 ± 1.0	62.96 ± 0.85	68.41 ± 0.55	72.10 ± 0.21	71.41 ± 0.50	71.05 ± 0.25	73.07 ± 0.85
20	59.48 ± 1.1	68.02 ± 0.74	73.22 ± 0.75	76.62 ± 0.11	76.60 ± 0.30	77.22 ± 0.50	81.22 ± 0.25
25	65.03 ± 1.1	74.17 ± 0.05	81.24 ± 1.0	83.36 ± 0.05	83.71 ± 0.80	85.02 ± 0.25	87.67 ± 0.25
30	71.80 ± 0.7	82.20 ± 1.0	84.79 ± 0.11	87.45± 0.50	89.05 ± 0.75	90.75 ± 0.45	96.35 ± 0.55

Using the ANOVA approach, the formulations were optimised depending on significant value. Which demonstrates that among batches F1 to F7, the F7 batch was the most adequate release. The F7 batch's ANOVA result was >0.005, which displays the highest significant value.

4.4 *In vitro* dissolution studies

These compressed tablets have average drug release percentages of 56.11 0.25 in 5 minutes and 96.35 0.55 in 30 minutes. It is determined that each parameter is suitable for further processing. Formulation F7, based on in vitro dissolution, demonstrated maximal drug release when utilising disintegrants (SSG and crospovidone). The final drug release kinetics were therefore chosen for this formulation.

Figure. 1. In vitro drug release profile of formulations F1-F4

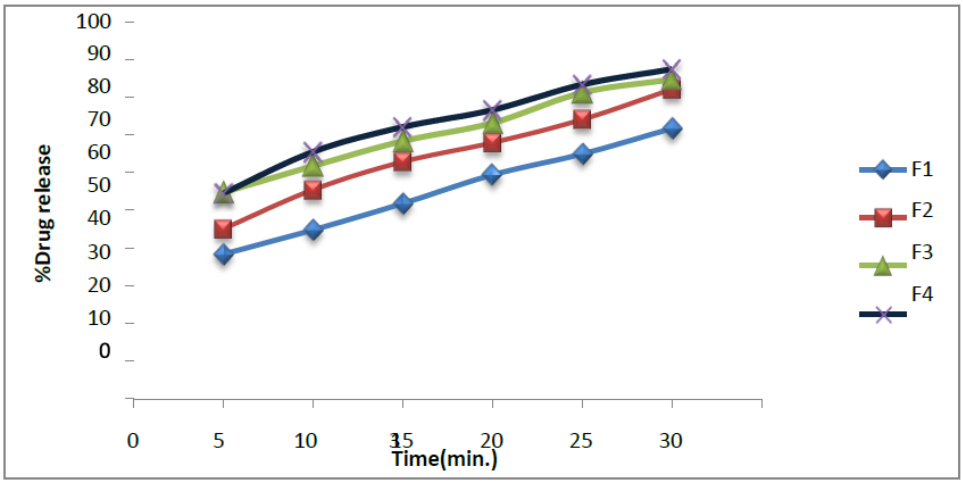
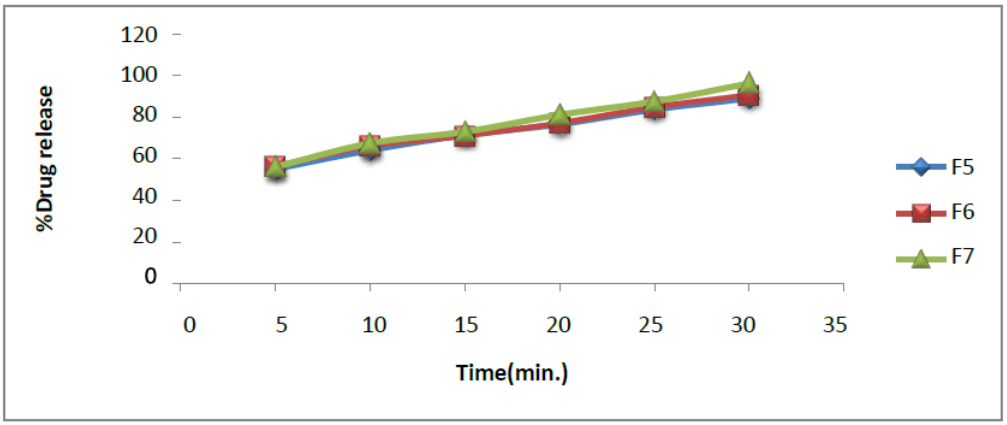


Figure. 2. In vitro drug release profile of formulations F5-F7



4.5. Drug release kinetics

The chosen formulation F7, which displays the plot of each model studied for drug release kinetics, was used for the release kinetics analysis. Based on the R2 value presented in table 4.4, it was found that zero order release kinetics was the most suitable.

Table 4.4 Regression coefficient (R^2) values

S. No.	Model	Regression (R^2)
1	Zero order release	$R^2 = 0.997$
2	First order release	$R^2 = 0.913$
3	Higuchi model	$R^2 = 0.99$
4	Korsmeyer – Peppas model	$R^2 = 0.949$

***Figure 3*: Zero order release kinetics plot of benzimidazole tablets**

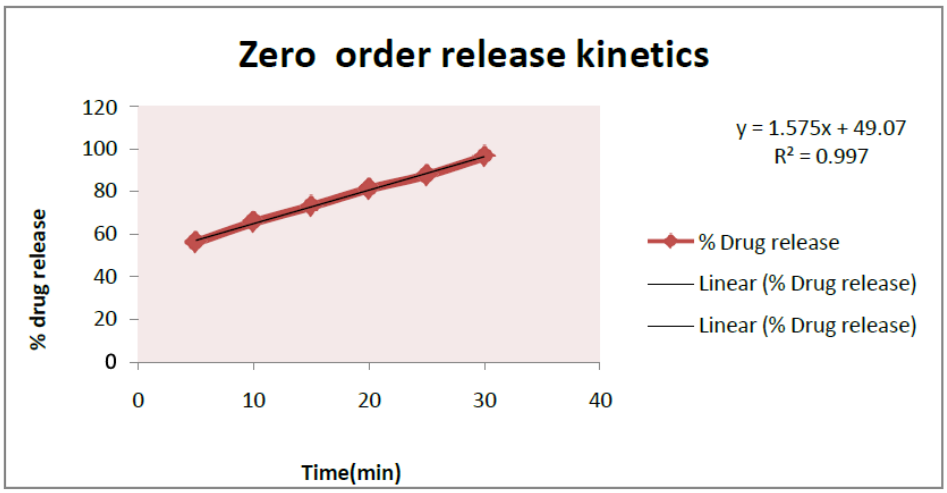


***Figure 4*: first order release kinetics plot of benzimidazole tablets**

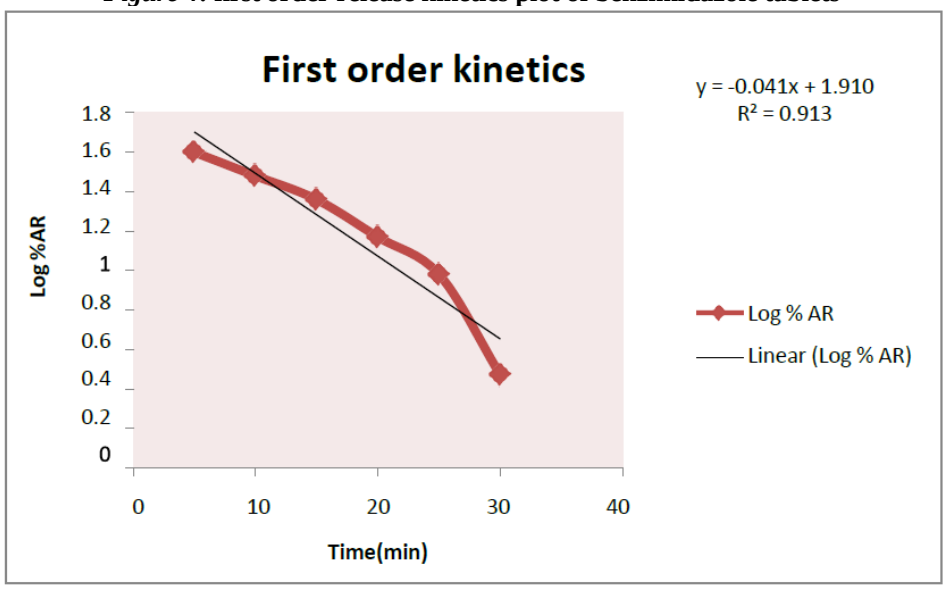


***Figure 5*: Higuchi model plot of benzimidazole tablets**

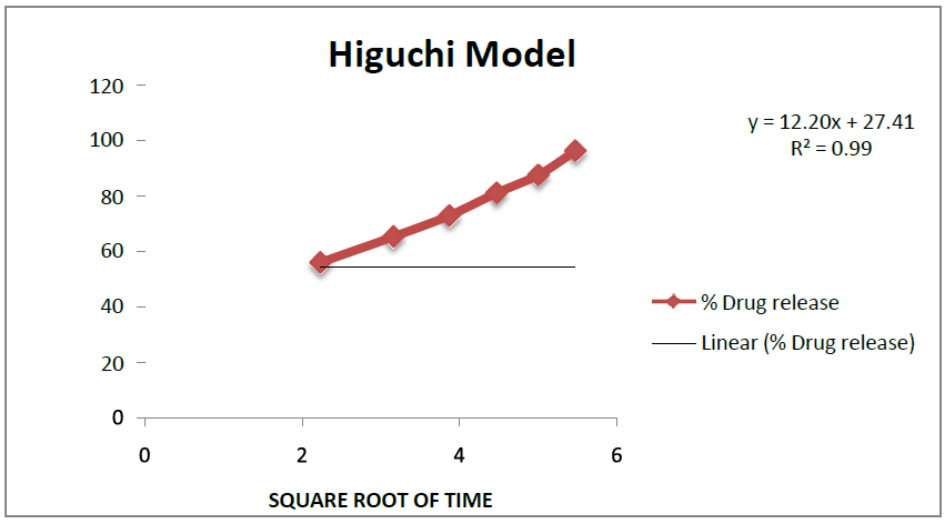
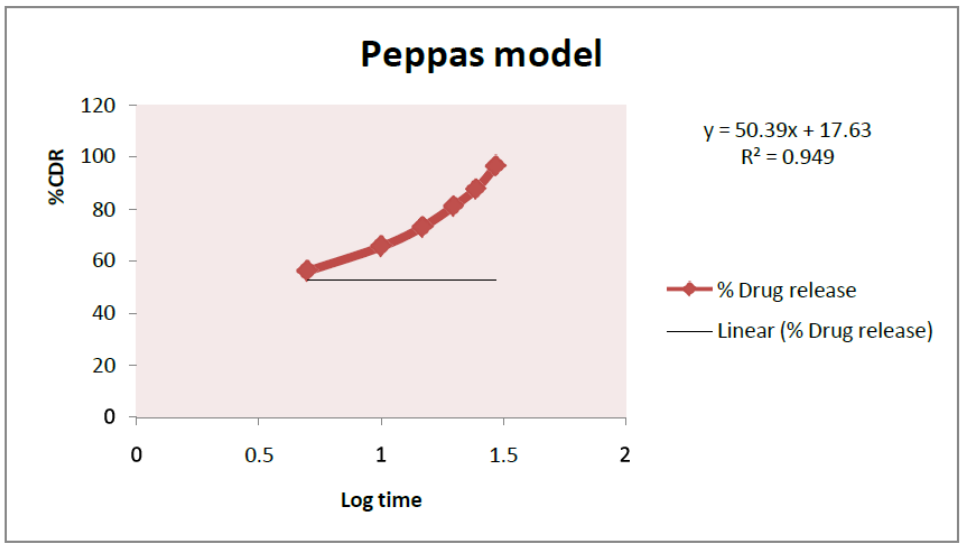


***Figure 6*: Korsmeyer – Peppas model plot of benzimidazole tablets**



V. CONCLUSION

The main objective of this research project was to develop and prepare an uncoated transmucosal fast-dissolving benzimidazole sodium drug delivery system for the treatment of GERD. To accomplish quick dispersion of tablets, two distinct super disintegrants—crospovidone and sodium starch glycolate—were tested. Since the drugs was released into the mouth cavity rather than the stomach, there was no need for any kind of covering to protect the drug from the acidic environment. This prevents the destabilising effect of PPIs on gastric juice and prevents the substantial hepatic metabolism that this class of drugs frequently causes.

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