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(RESEARCH ARTICLE)

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Formulation and evaluation of immediate release tablet of Cisapride

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Abstract

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. These tablets which disintegrate rapidly and get dissolved to release the medicaments. It may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release or absorption.

Keywords: Immediate; Cisapride; Fast acting; Oral; Dosage

1. Introduction

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose at a particular frequency. Thus drug may administered by variety routes in variety of dosage form.

Oral route is most common and popular route of administration of drug is oral route because of its systemic effect, patient compliance, less expensive to manufacture. Tablet provides high precision dosing. Tablet form is the most widely used dosage form because of self-administration and ease in manufacturing. In most of the cases immediate on set of action is required as compare to conventional therapy. To achieve the rapid onset of action and eliminate the drawbacks of conventional therapy immediate release dosage form is now a days popular and used as an alternative oral dosage form. Immediate release tablet are very quickly after administration. Basic approach used in development is the use of superdisintegrants which provide rapid disintegration of tablet after administration2.

1.1. Types of Tablets

1.1.1. Tablets ingested orally

- Standard Compressed tablet
- Multiple compressed tablet
    - Layered Tablet
    - Compression coated Tablet
- Repeat action Tablet
- Delayed action and enteric coated Tablet
- Sugar and chocolate coated tablet
- Film coated tablet
- Chewable Tablet

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- Targeted tablet
    - Floating tablet
    - Colon targeted tablet

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

1.1.2. Tablets used in the oral cavity

- Buccal Tablet
- Sublingual Tablet
- Troches and Lozenges
- Dental cones
- Mouth dissolved tablet

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

1.1.3. Tablets administered by other routes

- Implantation Tablet
- Vaginal Tablets

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

1.1.4. Tablets used to prepare solution

- Effervescent Tablet
- Dispensing Tablet
- Hypodermic Tablet
- Tablets Triturates

1.2. Immediate Release Dosage Form

Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation techniques6. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect7.

1.3. Advantages of Tablets

- They are unit dosage form, and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing.
- Accuracy and uniformity of drug content.
- Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).
- Usually taken orally, but can be administered sublingually, rectally or intra-vaginally.
- Their cost is lowest of all oral dosage form.
- They are the most compact of all oral dosage forms.
- They are in general the easier and cheaper to package and ship as compare to other oral dosage forms.
- Product identification is simple and cheap, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are ease to administer, does not require a specialist.
- They are better suited to large-scale production than other unit oral forms.
- They have the better properties of chemical, mechanical and microbiological stability.
- Easy to prepare.

- Provide prolonged stability to medicaments.
- Formulate as a special release products such as enteric or delayed release products.
- Easy to divide into halves and quarters whenever fraction dose is required.

1.4. Problems With Existing Oral Dosage Form

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.
- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.
- Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.
- Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.
- Cost of products is main factor as parenteral formulations are most costly and discomfort.

1.5. Desired Criteria For Immediate Release Drug Delivery System

- In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

1.6. Merits of Immediate Release Drug Delivery System

- Improved compliance/added convenience
- Improved stability, bioavailability
- Suitable for controlled/sustained release actives
- Allows high drug loading
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery
- Cost- effective
- Improved solubility of the pharmaceutical composition
- Decreased disintegration and dissolution times for immediate release oral dosage forms

2. Material and Methodology

Table 1 List of Materials

S. No	Materials	Use	Sources
1	Cisapride	Active Ingredient	Intas Pharmaceuticals Limited
2	Starch	Disintegerant and Binder	Universal Starch Chem Allied Limited.
3	Lactose	Diluent	Saputo Ingredients Inc.
4	Methyl paraben	Preservatives	Nebula Healthcare
5	Propyl paraben	Preservatives	Nebula Health Care
6	Talc	Lubricant	Neelkanth Minechem
7	Magnesium Stearate	Glidant	Legend Industries
8	Sodium starch glycolate	Super disintegerant	Maple Biotech Pvt. Ltd.

Table 2 List of Chemicals

1	Hydrochloric acid	Mercks Laboratories Pvt.Ltd
2	Sodium hydroxide	Mercks Laboratories Pvt.Ltd
3	Sodium sulphate	Mercks Laboratories Pvt.Ltd
4	Potassium hydroxide	Mercks Laboratories Pvt.Ltd
5	Potassium dihydrogen phosphate	Mercks Laboratories Pvt.Ltd

Table 3 List of Equipment

S. No	**Instrument Used**	**Manufacturer**
1	Electronic weighing balance	Mettler, Switzerland
2	Max mixer	Innofab India pvt.ltd,Hyderabad
3	Fluidized bed dryer	Alliance, Bombay
4	Cadmill	Cadmach, Ahemedabad
5	Tablet Compression Machine 45 stationdouble rotary	Cadmach, Ahemedabad
6	Friability Tester	Veego, Mumbai
7	Tablet Hardness Tester	Electrolab, Mumbai
8	Bulk density apparatus	Electrolab, Mumbai
9	Blender	Bhuvaneswari, Mumbai
10	Dissolution Apparatus	Veego, Mumbai
11	Tablet Disintegeration Apparatus	Veego, Mumbai
12	FT-IR Spectrophotometer	Perkin Elmer, USA

3. Results and discussion

3.1. Preformulation Studies of Cisapride

3.1.1. Organoleptic character

All the organoleptic character of paroxetine Hydrochloride was studied and it was found that all the character complies with USP standards.

Table 4 Characterization of Drug

Test	**Specification**	**Result**
Colour	White	Confirms
Odour	Odourless	Confirms
Physical State	Crystalline Powder	Confirms
Melting point	182^0C-185^0C	183^0C
Thin Layer Chromatography	Test Preparation is moreintense than StandardPreparation	Confirms
pH of Water Solution	4.5- 6.5	Confirms

3.2. The FTIR Spectrum of Cisapride

The FTIR absorption of Cisapride (Pure drug) were recorded in between 4000 to 400 cm^{-1}. Characteristics peak and chemical group present in IR spectrum of Cisapride was showed in .

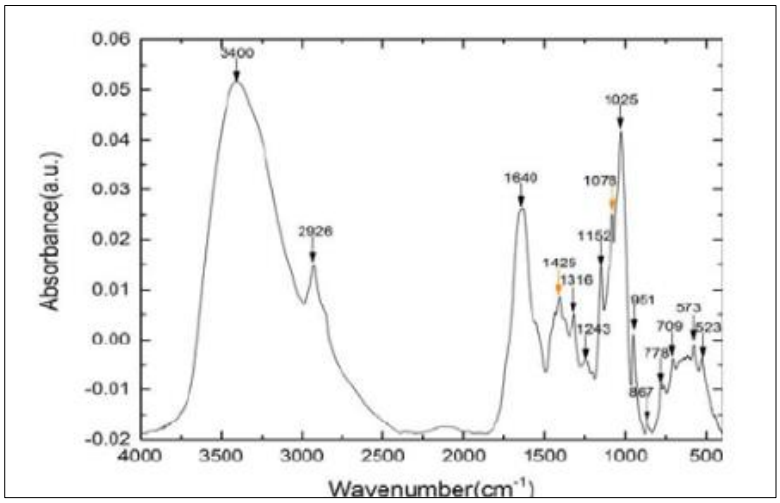

Figure 1 FTIR spectra of Cisapride

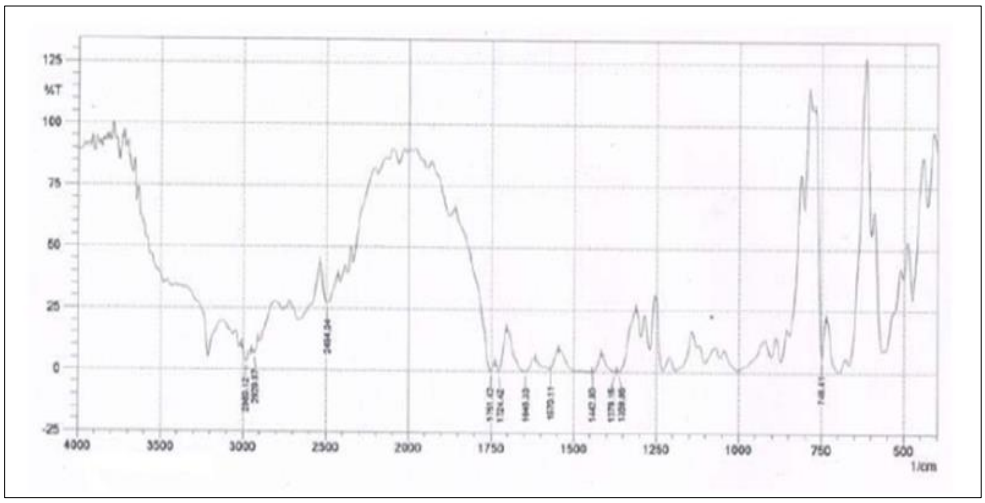

Figure 2 FTIR spectra of Cisapride and Excipient

The FTIR of drug and Starch shown intense band at 3413 cm-1, 1418 cm-1, 1024, 422cm-1 indicates no change in the functional groups NH, C=Cl and C=O, C-O. The FTIR of Drug and Lactose showed intense band at 3417 cm-1, 1500 cm-1, 1082, 528 cm-1.

Observed characteristics were N-H stretching at 3400 cm^1, CH

alkane stretching at 2926 cm^1, CO-NH stretching (C=0) at 1640 cm^1,

NH bending at 1425 c cm^1 and CN aromatic amine at1243 cm^1

As shown in fig. 1

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As shown in fig. 1

From the above interpretation it is understood that there is no major shifting in the frequencies of abovesaid functional groups. Hence these drug and excipients are compatible with each other.

3.3. Method of Drug Analysis

3.3.1. Construction of Calibration Curve in Deionized Water

As shown in the figure, the calibration curve of Cisapride follows linear relationship and the curve obeyed Beer-Lambert law within concentrationrange of 5-35 ugm/ml. The correlation coefficient value (R^2) was found to be 0.9987.

Table 5 Calibration curve in Deionized Water

SL. No	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.286
2	10	0.561
3	15	0.826
4	20	1.061
5	25	1.312
6	30	1.621
7	35	1.934

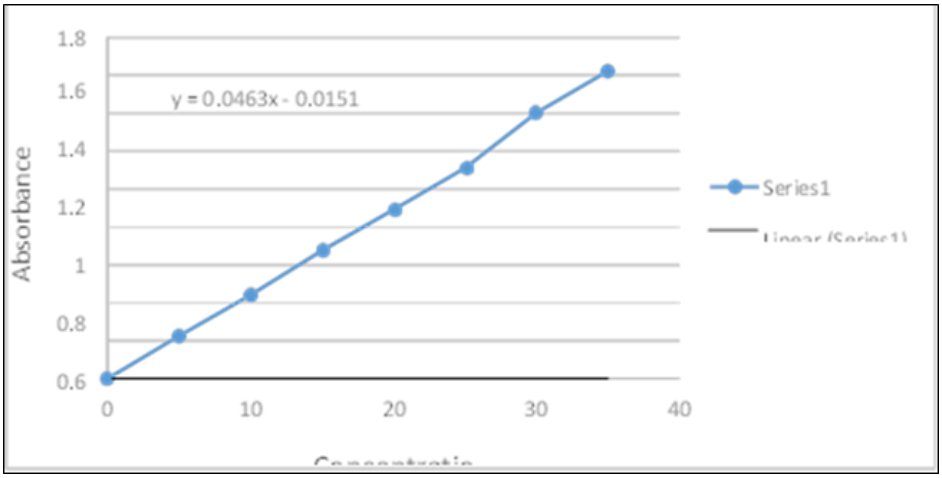

Figure 3 Calibration curve of Cisapride in Deionised water

3.4. In Phosphate Buffer pH 6.8

As shown in the figure, the calibration curve of Cisapride follows linear relationship and the curve obeyed Beer-Lambert law within concentrationrange of 5-35 ugm/ml. The correlation coefficient value (R2) was found to be 0.9987.

Table 6 Calibration Curve in Phosphate Buffer pH 6.8

Sl. No	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.224
2	10	0.442
3	15	0.676
4	20	0.891
5	25	1.11
6	30	1.402
7	35	1.622

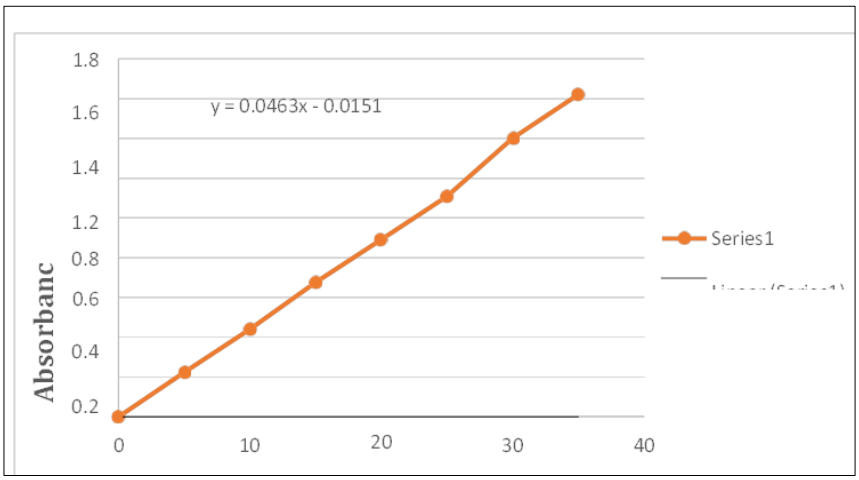

Figure 4 Calibration curve in phosphate buffer

3.5. In Stimulated Gastric pH (0.1N HCl)

Table 7 Calibration curve in simulated Gastric Fluid

SL. No	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.160
2	10	0.312
3	15	0.456
4	20	0.616
5	25	0.746
6	30	0.938
7	35	0.972

As shown in the figure, the calibration curve of Cisapride follows linear relationship and the curve obeyed Beer-Lambert law within concentrationrange of 5-35 (µgm/ml). The correlation coefficient value (R2) was found to be 0.9989.

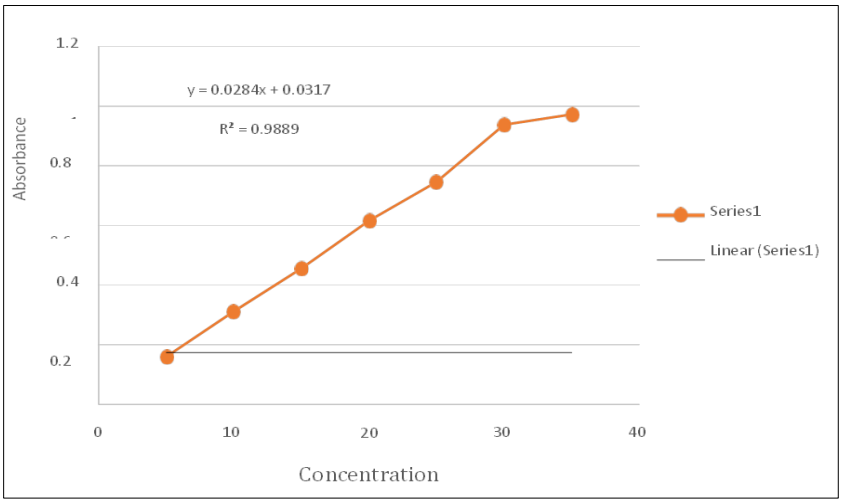

Figure 5 Calibration curve in simulated Gastric Fluid

3.6. Evaluation Parameters

3.6.1. Pre-compression parameters

The Cisapride granules was prepared and subjected to pre- compression parameters like bulk density, Tapped density, carr's index, sieve analysis and angle of repose. All the pre-compression parameters was evaluated and reported in table no: 8.6.

3.7. Bulk Density and Tapped Density

The bulk density of all the powder blend batch of Cisapride was found to be 0.59g/cm^3 to 0.66g/cm^{3}and the tapped density of the entire powder blend batch was found to be 0.71g/cm^3 to 0.80g/cm3showing good flow property.

3.8. Angle of Repose

The angle of repose of the drug and excipients was evaluated. The angle of repose of the entire powder blend of each formulation was found in between 25-29^0 which reveals the blend has a good flow property. Hence it is confirmed that all blends has free flow property.

3.9. Carr's Index

The measurement of free flowing powder can also be done by Carr's index. The Carr's index for all the formulations was found to be 12-14.6 which reveals that the blends have fair flow character.

3.10. Hausner Ratio

The Hausner ratio of drug and Excipients was done as per procedure. The hausner ratio of the entire powder blend of each formulation was found in between 1.14-1.2 which reveals that the blend is free flowing. So it is confirmed that all the blend has free flow property.

Table 8 Results of Pre-compression parameters

Parameters	Bulk Density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Angle of Repose (θ)	Hausner Ratio
F1	0.59	0.75	12	25.25	1.2
F2	0.63	0.73	13.69	26.27	1.15
F3	0.61	0.71	14.08	27.32	1.16
F4	0.60	0.70	13.79	26.65	1.16
F5	0.62	0.71	12.67	28.42	1.14
F6	0.64	0.74	13.51	29.96	1.15
F7	0.63	0.72	12.5	25.07	1.14
F8	0.66	0.76	13.15	26.56	1.15
F9	0.64	0.75	14.66	27.60	1.17

3.11. Sieve Analysis

The sieve analysis was determined by Mechanical sieve shaker. Since 80% drug particles were retained in sieve no 50, and about 18.5% of drug particles were retained on sieve no 18. Hence the particles lay between sieves no 50 and 18. The drug has a particle size lies between 297μm to 1mm.

Table 9. Particle size determination of Cisapride

SieveNo	Microns	Wt of drug + sieve (g)	Wt of the drug retained (g)	% of drug retained	Cumulative % of drug (μ) retained
#18	1000	389.7	3.7	18.5	18.5
#50	297	360	16	80	98.5
#70	210	331.3	0.3	1.5	100
#120	125	340	0	0	0
#140	105	338	0	0	0
#170	88	325	0	0	0
#200	74	320	0	0	0
#200Pass		460	0	0	0
			20	100	

3.12. Physical Stability of the Admixture

Table 10 Drug – Excipient stability profile

S. No	Items	1 Month/Control	1Month/ 600C
1	API	No change	No change
2	API+ Lactose	No change	No change
3	API+ Starch	No change	No change
4	API+ Talc	No change	No change
5	API+ Magnesium stearate	No change	No change

The drugs along with the excipients were kept under conditions specified and theresults are given. There was no physical change observed in the admixture after one month at 60 ºC

3.13. Post Compression Parameters

The tablets of different formulations of Cisapride were subjected to various evaluation tests, such as hardness, thickness weight variation, friability and drug content. All the result is shown in Table 8.9.

3.14. Thickness

The thickness of the tablets was found out using Vernier Caliper and the thickness found to be in the range of 4.02-4.12mm for the uncoated tablets (F1-F6). For the enteric coated tablets the thickness ranged from 4.21-4.30.Thus all formulations showed uniform thickness.

3.15. Hardness test

The hardness of tablet was measured by Monsanto hardness tester. Ten tablets from the batch were used for hardness studies and results showed they were in between 3.5- 4.2 Kg/cm2.

3.16. Weight variation test

In a weight variation, the pharmacopoeial limit for the percentage deviation for tabletsof more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformityof weight as per official requirements.

3.17. Friability test

The Friability of all the formulation was below 1% as per IP specification.

3.18. Wetting Time

The wetting time of tablet was measured and the result found in between 35- 45 seconds.

3.19. Drug content analysis

Cisapride tablet was tested for their drug content and all the formulation showed drug content 90 to 110%.

All the tablet formulations showed acceptable pharmaco-technical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

Table 11 Results of post compression parameters

Evaluation of Post Compression Parameter							
Formulation Code	**Hardness (kg/cm^2)**	**Friability (%)**	**Weight variation Test (%) ±S.D**	**Uniformity of Drug Content (%) ± S.D**	**Thickness of Tablets (mm) ± S.D**	**Wetting Time (Seconds)**	**Disintegration Time (sec) ± S.D**
F1	3.7	0.69	102.3±0.15	98.94±0.25	2.7	36	42±0.73
F2	3.9	0.71	101.2±0.66	99.46±0.24	2.7	39	51±0.58
F3	4.2	0.68	98.9±0.301	99.65±0.33	2.7	45	55±0.65
F4	3.6	0.71	100.6±0.23	99.45±0.12	2.7	38	34±0.59
F5	3.5	0.74	102.1±0.18	99.25±0.31	2.7	40	41±0.85
F6	4.1	0.72	101.3±0.26	99.52±0.06	2.8	43	45±0.71
F7	3.7	0.69	101.6±0.22	99.86±0.39	2.7	35	30±0.64
F8	3.9	0.71	99.5±0.18	99.78±0.35	2.7	39	32±0.48
F9	4.1	0.70	100.8±0.21	99.42±0.14	2.8	42	35±0.40

3.20. Drug Release Study

3.20.1. Innovator drug release profile

Cumulative percent drug released from the tablet were shown

Table 12 *In-vitro* Drug release profile of Innovator

S. No	Time (Min)	Percentage cumulative drug release
1	3	35.50
2	6	46.40
3	9	79.40
4	12	92.68
5	15	99.58

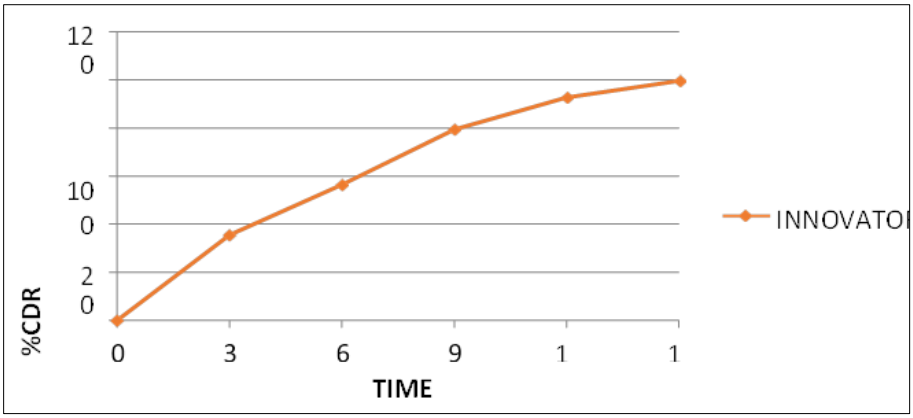

Figure 6 *In-vitro* Drug release profile of Innovator

4. Conclusion

The Present study was conducted to formulate and evaluate the immediate release tablet of Cisapride. Pre-formulation study was carried out initially with study of selection of superdisintegrants was done and different formulations were prepared using sodium starch glycolate and starch as disintegerants. Immediate release tablet of Cisapride was prepared by wet granulation method. The tablet disintegrated rapidly and has an acceptable friability and hardness. *In vitro* drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based on immediate release tablet of Cisapride would be quite effective in emesis, providing quick onset of action on administration.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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