World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

FORMULATION AND INVITRO EVALUATION OF ROFLUMILAST ORALLY DISINTEGRATING TABLET

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Received: 01-11-2024 / Revised Accepted: 09-11-2024 / Published: 19-11-2024

ABSTRACT:

An Orally disintegrating tablet disperses readily in saliva and the drug is available in solution or suspension form for the immediate absorption and resulting in rapid onset of action. In the present research work Roflumilast Oral disintegrating tablet were prepared by Direct Compression Technique using varying concentrations of Croscarmellose Sodium, Crospovidone and Ludiflash as super disintegrants. The formulations prepared were evaluated for precompression & post compression parameters. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Roflumilast) and optimized formulation (Roflumilast+ excipients) which indicates there are no physical changes. Post compression parameters was found to be within the limits. Among the formulation prepared the tablet containing 2.5 mg concentration of Ludiflash shows 99.85±1.46% of the drug release within 30 min & follows first order kinetics. The overall result indicated that the formulation F12 containing Ludiflash is better and fulfilling of the needs of the Orally disintegrating tablet.

Key words: Orally disintegrating tablets, Direct Compression Technique, Roflumilast, Ludiflash, FTIR.

INTRODUCTION

Recent advances in new drug delivery systems attempt to increase the safety and efficacy of the medication molecule by developing a dosage form suitable for administration. Orally disintegrating tablets (ODTs) are solid dosage forms that dissolve or disintegrate quickly in the oral cavity, resulting in a solution or suspension that does not require water. These are newer varieties of tablets that dissolve in saliva within a few seconds. Oral disintegration tablets have several benefits over normal pills [1]. Dysphasia is a widespread condition in all age groups, particularly among the elderly and children, due to physiological changes associated with those groups. When it comes to oral solid dose forms, such issues result in a high rate of noncompliance and ineffective therapy. Nowadays, there is a growing interest in developing not just rapid dissolving tablets to make swallowing easier, but also orally decomposing pills that are designed to dissolve quickly in your mouth.

ODTs provide an advantage for the population who have trouble swallowing traditional pills or capsules, bedridden, mentally ill, and recalcitrant people suffering from nausea, motion sickness, abrupt bouts of allergic reaction, or coughing [2]. The key features of this dosage form, in terms of patient compliance, quick onset of action, higher bioavailability, superior stability, and pleasant flavor, enhance the acceptability of bitter tasting medications, making these tablets popular as a dosage form of choice in the present market [3]. The usage of super disintegrants is the fundamental strategy to developing an oral disintegration tablet. Because of the presence of super disintegrants, it dissolves fast, resulting in rapid drug absorption and, consequently, rapid beginning of action. Because absorption occurs straight from the mouth, avoiding first-pass metabolism, the drug's bioavailability rises. Natural disintegrants such as gum karaya, modified starch, agar, and synthetic disintegrants such as microcrystalline cellulose, crospovidone, croscarmellose sodium, sodium starch glycolate, etc. have been used in the formulation of fast dissolving tablets at concentrations of up to 10% by weight relative to the total weight of the dosage form [4]. Throughout modern history, several procedures have been used to manufacture orodispersible tablets, including freeze drying or lyophilization, spray drying,

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How to Cite this Article V Naga Keerthi Priya. FORMULATION AND INVITRO EVALUATION OF ROFLUMILAST ORALLY DISINTEGRATING TABLET, World J Pharm Sci 2023; 12(04): 28-37; https://doi.org/10.54037/WJPS.2022.100905.

molding, sublimation, mass extrusion, and direct compression [5]. This direct compression approach is preferred over other methods of producing orodispersible tablets because to its inexpensive manufacturing costs, use of standard equipment, and fewer processing stages.

COPD, which now affects more than 200 million people globally, presents as a gradual deterioration to the lung integrity with varied clinical symptoms and intricate pathophysiologic causes [6].

Abnormal immune responses and severe inflammation in the lung airways are linked to the onset and development of COPD. The infiltration of innate and adaptive inflammatory cells into the local lung tissue is regarded as the primary pathogenic component in COPD patients. Furthermore, available information suggested that the neutrophil-to-lymphocyte ratio (NLR) might predict the course and prognosis of COPD [8].

Asthma is another refractory inflammatory airway illness that is characterized by bronchial hyperreactivity, mucus production, airway constriction and remodeling, as well as an expansion of inflammatory cells, particularly neutrophils[9,10] Undoubtedly, COPD and asthma patients have similar clinical characteristics, and it is difficult to identify asthma from COPD, especially when they coexist in older individuals [11].

In the past decades, PDE4 inhibitors used in the Pharmacists are becoming increasingly interested in treating COPD and asthma. Inhibition of PDE4 significantly reduces airway inflammation and relaxes smooth muscle via increasing the amount of cAMP.

Roflumilast is a selective, long-acting PDE-4 inhibitor that was authorized in 2010 to treat inflammatory lung disorders such as asthma and chronic obstructive pulmonary disease.

Roflumilast (brand name Daxas) was permitted for the treatment of severe COPD and asthma symptoms in the EU and USA in 2010 and 2011, respectively, making it the first PDE4 inhibitor to be authorized. Roflumilast has been researched as a strong anti-inflammatory medication that regulates airway inflammation[12,13]. In vitro, roflumilast inhibited PDE4 activity (IC50 = 0.8 nM) in human neutrophils with high selectivity. This showed excellent anti-inflammatory potential in fMLP-induced leukotriene B4 (LTB4) and reactive oxygen species (ROS) formation in human neutrophils, lipopolysaccharides (LPS)-induced tumor necrosis factor α (TNF-α) synthesis in monocytes, dentritic cells, and cytokines production in anti-CD3/CD28-stimulated CD4+ T cells.

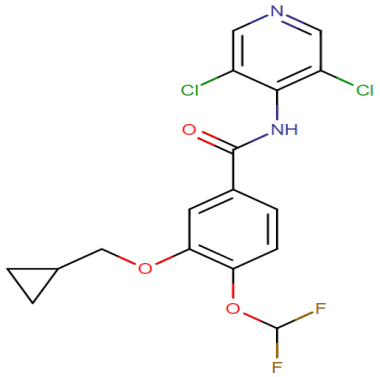

Figure No.1 Structure of Roflumilast

MATERIALS & METHODS USED: Roflumilast API was procured from Kekule Pharma Limited, and Ludiflash, Croscarmellose sodium, Crospovidone, Aspartame, Mannitol were procured from Signet Chemical Corp., Mumbai, Talc, Magnesium stearate were procured from S.D. Fine Chem. Ltd., MCC was procured from Aurbindo Pharma Ltd., Hyd.

Formulation of Oral Disintegrating Tablets of Roflumilast:

Table No.1 Formulation Table

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Roflumilast	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Croscarmello	1	1.5	2	2.5	--	--	--	--	--	--	--	--
Crospovidone	--	--	--	--	1	1.5	2	2.5	--	--	--	--
Ludiflash	--	--	--	--	--	--	--	--	1	1.5	2	2.5
Mannitol	50.5	50.0	49.5	49.0	50.5	50.0	49.5	49.0	50.5	50.0	49.5	49.0
M.C.C	40	40	40	40	40	40	40	40	40	40	40	40
Aspartame	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight(mg)	100	100	100	100	100	100	100	100	100	100	100	100

Procedure: The Roflumilast oral disintegrating tablets were prepared using super disintegrants by direct compression method. Roflumilast tablet each weighing 250 mg containing 100 mg of Roflumilast was formulated as follows, All the ingredients were passed through #60mesh sieve separately. The drug & Mannitol were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3.5-5 kg/cm2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F12 (100 mg).

RESULTS & DISCUSSION

Solubility studies:

Solubility of Roflumilast was carried out at 25ºC using 0.1N HCl, 6.8 phosphate buffer, 7.4pH buffer and purified water.

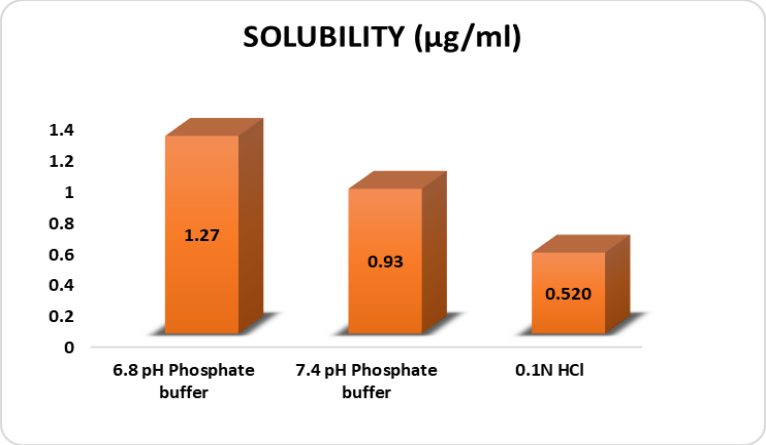

Figure No.2 Solubility studies

Discussion: From the above conducted solubility studies in various buffers, we can say 6.8 pH phosphate Buffer has more solubility when compared to other buffer solutions.

Determination of λ_{max}:-

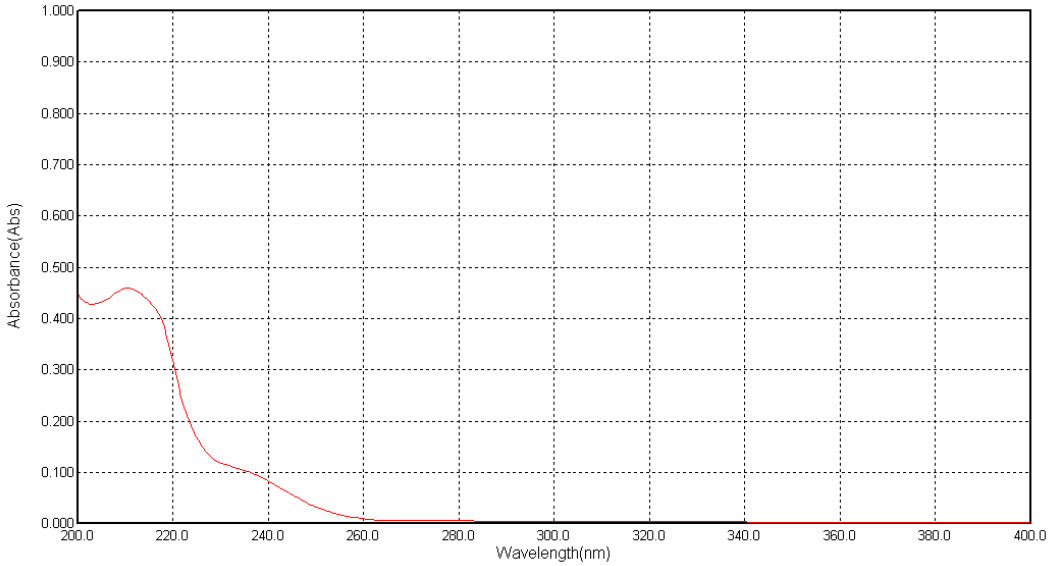

Figure No.3 UV Spectrum curve of Roflumilast

Discussion: The Absorption maxima of Roflumilast drug in the 100% concentration by using 6.8 pH Phosphate buffer was found to be at 213 nm by using Single Beam Spectrophotometer (YIS-294).

Calibration curve of Roflumilast in 6.8 pH phosphate Buffer

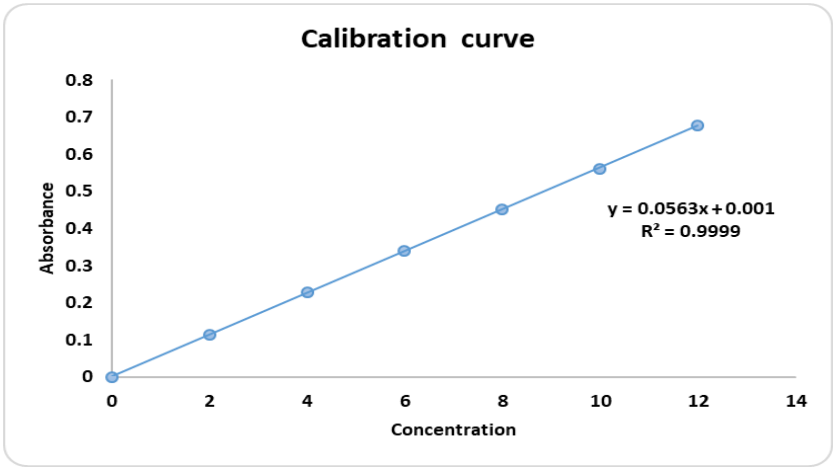

Figure No.4 Standard graph of Roflumilast

Discussion: The linearity was found to be in the range of 2-12µg/ml in pH 6.8 phosphate buffer. Regression analysis was selected because it minimizes the deviation and correct the variance heterogeneity. The regression line was defined by its slope (m) and its intercept (C) for normal regression analysis was found as = 0.0563x + 0.001, with regression coefficient of 0.9999 respectively. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

FTIR STUDIES:

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

PURE DRUG:

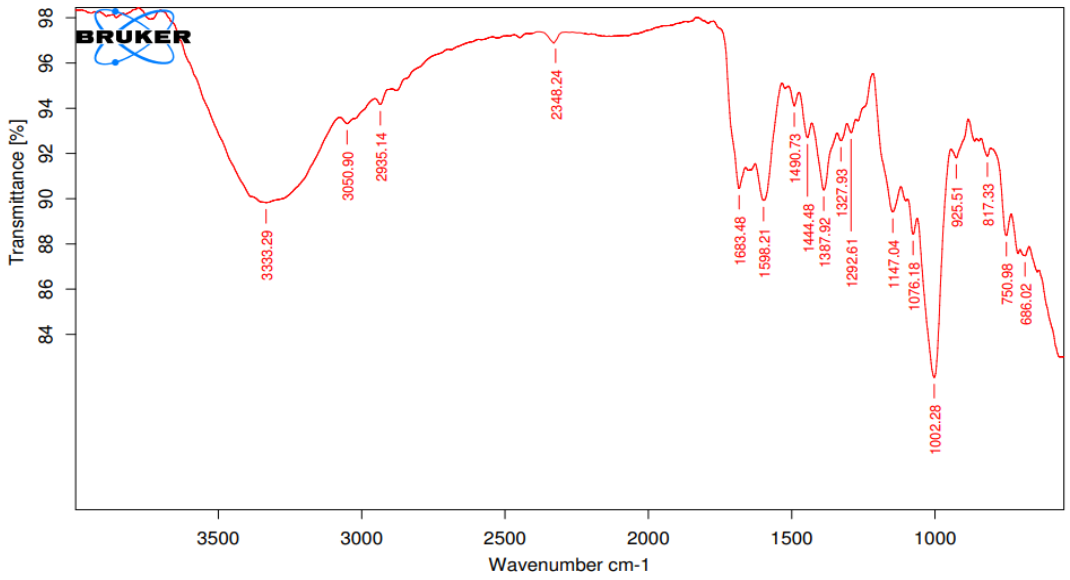

Figure No.5 IR spectrum of Roflumilast

Optimized formulation:

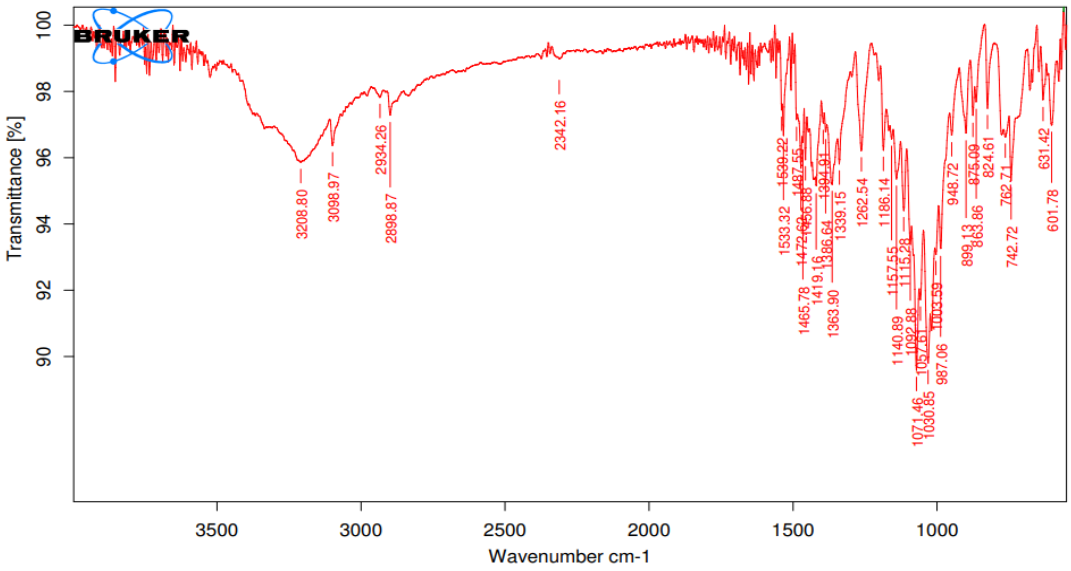

Figure No.6 IR spectrum of Optimized formulation

Discussion:

The FTIR spectrum of pure Roflumilast, prepared Oral Disintegration Tablets of Roflumilast formulation by Direct Compression Techniques are shown in Figure respectively. From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Roflumilast) and optimized formulation (Roflumilast + excipients) which indicates there are no physical changes.

Characterization of blend:

Table No.2 Pre-Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean± SD)	Tapped density (mean± SD)	Angle of repose (mean± SD)	Carr's index (mean± SD)	Hausner's ratio (mean± SD)
F1	0.215±0.005	0.304±0.004	24.58±0.42	17.28±1.17	1.16±0.07
F2	0.218±0.006	0.317±0.006	25.87±0.16	16.20±1.34	1.15±0.08
F3	0.234±0.002	0.327±0.003	27.65±0.25	15.43±1.45	1.14±0.07
F4	0.246±0.007	0.336±0.004	26.66±0.37	15.12±1.28	1.13±0.06
F5	0.210±0.006	0.312±0.003	23.85±0.18	16.43±1.67	1.17±0.08
F6	0.206±0.007	0.324±0.004	24.58±0.43	15.25±1.43	1.17±0.07
F7	0.227±0.004	0.337±0.009	25.29±0.20	14.46±1.45	1.15±0.06
F8	0.234±0.006	0.345±0.006	26.45±0.53	13.20±1.28	1.14±0.08
F9	0.224±0.002	0.321±0.007	24.55±0.36	15.74±1.17	1.15±0.08
F10	0.218±0.003	0.332±0.003	25.66±0.45	14.36±1.64	1.14±0.06
F11	0.246±0.004	0.341±0.006	26.85±0.28	13.42±1.38	1.13±0.07
F12	0.251±0.002	0.367±0.005	27.97±0.37	11.18±1.74	1.11±0.05

Discussion: The angle of repose of different formulations was ≤ 27.97±0.37, which indicates that material had good flow property. So, it was confirmed that the flow property of blends was free flowing. The bulk density of

blend was found between 0.206±0.007 g/cm^3 to 0.251±0.002 g/cm^3. Tapped density was found between 0.304±0.004 g/cm^3 to 0.367±0.005 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.18±1.74-17.28±1.17 and Hausner's ratio from 1.11±0.05-1.17±0.07 which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Table No.3 Characterization Roflumilast oral disintegrating tablets

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegration time(sec)
F1	100.7±0.04	2.7±0.07	4.2±0.06	0.48±0.05	17±1
F2	101.6±0.02	2.8±0.05	4.4±0.07	0.51±0.04	15±2
F3	99.5±0.10	2.9±0.06	4.6±0.05	0.53±0.08	14±1
F4	101.8±0.08	3.0±0.04	4.7±0.08	0.56±0.06	13±1
F5	102.3±0.07	2.5±0.03	4.4±0.03	0.50±0.04	16±1
F6	102.6±0.07	2.6±0.08	4.5±0.04	0.53±0.05	15±2
F7	100.4±0.05	2.8±0.05	4.6±0.06	0.59±0.04	13±2
F8	101.9±0.07	2.9±0.06	4.8±0.08	0.62±0.04	12±1
F9	102.2±0.03	2.9±0.04	4.3±0.07	0.54±0.06	14±2
F10	99.4±0.05	3.2±0.07	4.5±0.05	0.59±0.03	13±1
F11	98.6±0.07	3.3±0.06	4.6±0.03	0.66±0.08	12±1
F12	100.7±0.09	3.5±0.08	4.9±0.04	0.73±0.05	10±1

Discussion: Hardness of the tablet was acceptable and uniform from batch-to-batch variation, which was found to be 4.2±0.06– 4.9±0.04 kg/cm^2 and thickness was found to be 2.7±0.07-4.9±0.04 mm. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F12 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Disintegration time as per IP, for all the formulations was found to be between 17±1-10±1 seconds, which was well within IP limit. Formulations with Ludiflash as super disintegrants shows quicker disintegration among all the formulations. Ludiflash with concentration as a super disintegrant shows very less disintegration time.

Drug content uniformity of formulations:

Table No.4 Drug content uniformity of formulations F1-F12

Formulation	% of Drug content
F1	92.18±1.37
F2	94.43±1.45
F3	96.26±1.27
F4	97.48±1.68
F5	94.56±1.15
F6	95.28±1.19
F7	97.45±1.37
F8	98.17±1.46
F9	97.25±1.28
F10	98.67±1.75
F11	98.48±1.38
F12	99.25±1.46

Discussion: % Drug content values of formulation F1 – F12 was found to be in the range of 92.18±1.37-99.25±1.46%

Dissolution studies: The prepared tablets were subjected to dissolution studies in order to know the amount drug release. As the concentration of super disintegrant increased, the drug release time decreased.

Table No.5 % Cumulative drug release of formulations F1-F6

Time (Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	24.78 ±1.45	30.28 ±1.54	41.37 ±1.41	47.37 ±1.46	26.27 ±1.46	32.17 ±1.67
10	37.75 ±1.64	38.15 ±1.95	53.25 ±1.18	56.85 ±1.14	41.38 ±1.45	41.42 ±1.54
15	56.86 ±1.84	47.48 ±1.67	67.43 ±1.12	69.37 ±1.20	58.36 ±1.49	53.16 ±1.20
20	77.38 ±1.57	56.26 ±1.57	75.56 ±1.38	78.69 ±1.20	67.52 ±1.16	67.25 ±1.65
25	86.21 ±1.78	87.18 ±1.29	87.25 ±1.48	86.41 ±1.28	76.43 ±1.28	79.41 ±1.84
30	94.44 ±1.62	96.48 ±1.58	97.37 ±1.15	98.14 ±1.62	93.67 ±1.45	95.84 ±1.26

Table No.6 % Cumulative drug release of formulations F7-F12

Time (Min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	**0**
5	37.63 ±1.48	46.94 ±1.48	42.25 ±1.45	45.56 ±1.27	53.67 ±1.42	**57.84 ±1.25**
10	46.67 ±1.25	55.64 ±1.16	58.37 ±1.10	61.45 ±1.38	65.32 ±1.18	**68.67 ±1.25**
15	58.74 ±1.63	69.25 ±1.48	65.46 ±1.20	73.45 ±1.17	74.45 ±1.39	**74.41 ±1.16**
20	71.45 ±1.20	83.64 ±1.48	77.75 ±1.34	85.65 ±1.25	79.45 ±1.84	**88.47 ±1.24**
25	86.42 ±1.15	91.15 ±1.25	86.46 ±1.68	91.75 ±1.56	93.41 ±1.26	**95.45 ±1.26**
30	96.38 ±1.42	97.75 ±1.25	96.25 ±1.34	97.38 ±1.49	98.37 ±1.46	**99.85 ±1.46**

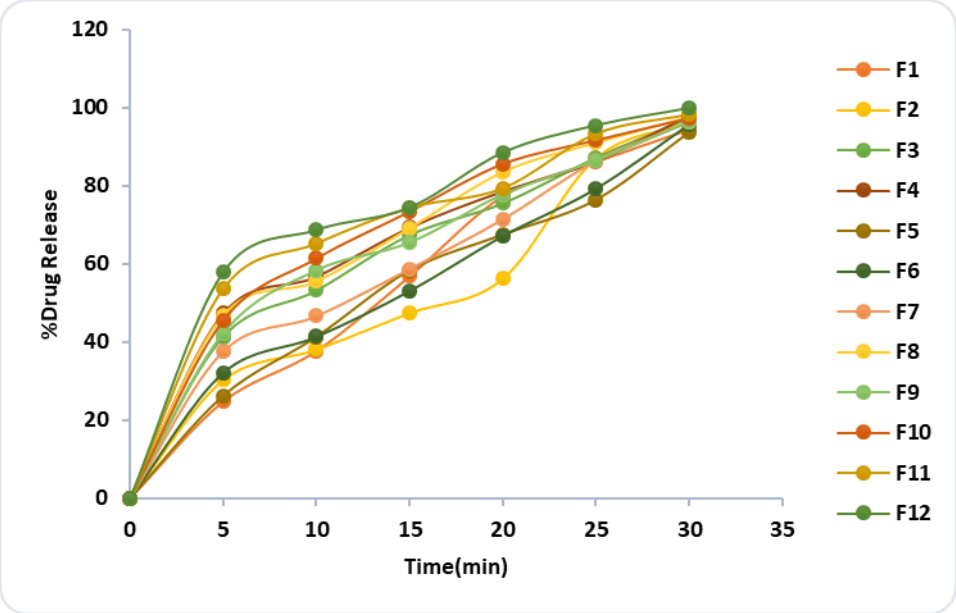

Figure No.7 % Drug Release of Formulation F1 –F12

Discussion: By comparing the dissolutions profiles of formulations F1-F12 containing super disintegrants in the concentrations of (1mg, 1.5mg, 2mg, 2.5 mg), the drug release was not found to be satisfactory Ludiflash shows satisfactory drug release at the end of 30mins. Among all the formulations F12 containing 2.5mg Ludiflash shows 99.85±1.46% drug release at the end of 30min. So F12 formulation was considered as the optimized formulation. Further kinetics were measured for F12 formulation.

DRUG RELEASE KINETICS STUDIES:

ZERO ORDER:

Figure No:8 Zero order plot of Roflumilast F12 Formulation

FIRST ORDER:

Figure No:9 First order plot of Roflumilast F12 Formulation (Time Vs Log% ARA)

Table: Order of kinetic values of Formulation F12

Order of kinetics	Zero order	First order
Regression values	0.800	0.803

Discussion: The drug release from the oral disintegrating tablets was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation **F12** follows First order drug release.

SUMMARY

The present study is an attempt to select the best possible diluent - disintegrant combination to formulate Oral disintegrating tablets of Roflumilast, which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action. Croscarmellose Sodium, Crospovidone and Ludiflash, were used as disintegrants. In all the formulations, and Magnesium stearate and talc were used as lubricant and glidant respectively. The results of the drug – excipient compatibility studies revealed that there was no chemical interaction between the pure drug and excipients. Direct Compression Technique was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the formulations showed acceptable flow properties. The post compression parameters like the hardness, thickness, friability and weight variation, disintegration time, disintegration time in oral cavity and In vitro release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 92.18±1.37-99.25±1.46% of Roflumilast, which was within the acceptable limits. Among all the formulations F12 shows 99.85±1.46% drug release at the end of 30min. F12 contains Ludiflash (2.5mg), it shows better % drug release when compared to other formulations. So, F12 was considered as the optimized formulation. The drug release kinetics shows that the optimized formulation F12 follows First order drug release.

ACKNOWLEDGEMENT
The authors are thankful to the Department of Pharmaceutics, Srinivasarao college of Pharmacy, Visakhapatnam, Andhra Pradesh, Affiliated to Andhra University, Visakhapatnam, Andhra Pradesh, India and Spectrum Pharma Research Solutions, Hyderabad, Telangana, India.

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