ISSN 2515-8260 Volume 9, Issue 7, Summer 2022

SOLUBILITY ENHANCEMENT OF ORALLY DISINTEGRATING TABLETS OF PRANLUKAST BY SOLID DISPERSION TECHNIQUE

M.Pradeep Kumar[1]*, Uttam Prasad Panigrahy[2], Satyabrata Jena [3],

Karthickeyan Krishnan[4],S Prema[5] , Rutuja Sonawane[6]

[1]Professor, Department of Pharmaceutics, Vasavi institute of Pharmaceutical sciences, Kadapa-516247

[2]Associate Professor, Department of Pharmaceutical Analysis, Faculty of Pharmaceutical sciences, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India- 781026

[3]Associate Professor, Department of Pharmaceutics, Bhaskar Pharmacy college, Yenkapally, Moinabad, Ranga Reddy, Hyderabad, Telangana 500075

[4]Professor and Head, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai 600117, Tamil Nadu, India

[5]Assistant professor, Crescent School of Pharmacy, B.S. Abdur Rahman Crescent Institute of Science and technology, vandalur, Chennai 600048

[6]Research Scholar, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced studies, VISTAS, Pallavaram, Chennai, Tamilnadu, India. Assistant Professor, Department of Pharmaceutical Chemistry, SCES'S Indira College of Pharmacy, Pune, Maharashtra, India.

Corresponding author Email: pradeepbadvel98@gmail.com

ABSTRACT

Pranlukast is a drug in the BCS class II category, and its absolute bioavailability is around 4.3%. PEG 4000 and PEG 6000 were used in the development of the pranlukast solid dispersion with oral disintegrating tablet to boost the drug's biological performance. Multiple carriers were used to create solid dispersions of pranlukast (1:0.25, and 1:0.5). Solvent evaporation prepared Pranlukast solid dispersions were discussed in relation to studies examining their solubility, melting point, drug content uniformity, entrapment efficiency, and in vitro dissolution. The solid state was characterised using a variety of analytical techniques, including FT-IR studies. Following a thorough analysis of all four formulations (SF1-SF4), it was concluded that formulation(SF4) containing Pranlukast+ PEG 6000 (1:0.5) showed the best results by solvent evaporation method at the end of 90 min with drug release of 82.96 percent. Changes in disintegrant concentration allowed the optimised formulation to be used to create immediate release tablets. Prior to and following compression, extensive analysis was performed on the

input parameters. These results are all within a reasonable margin of error. The effectiveness of the tablets' drug delivery was evaluated in a laboratory dish using a buffer with a pH of 6.8. Cross caramellose sodium (7.5mg) is used in Formulation F6, and it results in a 98.02 percent drug release in 40 minutes. Zero order release kinetics is essential for the best formulation.

Keywords: Pranlukast, PEG 4000, PEG 6000, Crosscarmellose Sodium

INTRODUCTION

The design of dosage forms is becoming increasingly focused on patient compliance and ease of administration. Creating drug delivery systems that are both aesthetically pleasing and safe for patients has become a priority in recent years [1]. Oral dosage forms have not been overtaken in popularity despite the introduction of numerous novel and advanced drug delivery systems for therapeutic use [2]. In terms of patient compliance, ease of use, and medicine production costs, oral administration of drugs continues to dominate. Orally disintegrating tablets (ODTs) [3] are a novel dosage form developed by formulators to address these medical needs. Some ODTs boast a higher bioavailability than conventional tablets [4]. Poor solubility is a major problem in modern drug development; it is estimated that the vast majority of drugs currently on the market are either not soluble in water or only slightly soluble. .

Difficulty swallowing, also known as dysphagia, affects people of all ages. The prevalence of dysphagia is about 35%, as reported by Sastry et al. [5].

Patients of all ages, especially the elderly and the young, and travellers who may not always have access to water require dosage forms that are simple to swallow. According to the research, roughly half of the population has this issue [6].

Since the drug is dispersed entirely in the oral cavity, it is imperative that the active ingredients in these systems be taste-masked. Because they lack the necessary mechanical strength, it is crucial that freeze-dried and effervescent disintegrating systems dissolve quickly upon coming into contact with fluids. Likewise, drugs that are easily destroyed by heat cannot be made using the candy process. ODTs formed by these methods can have varying mechanical strength of tablets, flavour and mouth feel, swallowability, drug dissolution in saliva, bioavailability, and stability [7] due to the different approaches taken in their development.

Large-scale dispersal Chiou and Reigelman first defined solid dispersion as "dispersion of one or more active ingredients in an inert carrier or matrix (hydrophilic) at solid state prepared by fusion, solvent, or melting solvent method" [8-10]. Alternately, "a dispersion that include the formation of eutectic mixtures of drug with carriers that soluble in water easily by melting of their physical mixtures" [11, 12] describes a solid dispersion.

As an antagonist for cysteinyl leukotriene receptor-1, pranlukast helps reduce inflammation. It counteracts or mitigates bronchospasm brought on by an allergic reaction to inadvertently or unintentionally encountered allergens, a condition most commonly seen in asthmatics.

MATERIALS AND METHOD

Pranlukast was received as a gift from Candila Pharmaceutical Laboratories, while PEG 4000, PEG 6000 Methanol was acquired from S. D. Fine Chemicals. Crospovidone Crosscarmellose Sodium, Mannitol, MCC, and Magnesium Stearate Talc manufactured in Hyderabad by B.M.R. Chemicals. All remaining chemicals were of analytical grade**.**

METHODOLOGY

Sample preparation

Potassium bromide was allowed to dry out completely before being pound into a powder in a mortar. Digital scale readings were used to combine and powder about 2% of the drug sample. The dehumidifier had two discs of stainless steel taken out of it. Next, we placed a piece of cardboard with a hole cut out of it on top of one of the discs (we kept these in the tin can next to the oven) and filled the hole with the finely ground mixture.

The hydraulic press has a second stainless steel disc that transports the sandwich to the pistil. The hydraulic pump's handle was lowered with a downward pumping motion. When the pump chamber is full, the pistil will rise to the very top. Then, we increased the pressure by raising the pump's handle, which we did until we reached 20,000 psi. After a moment, the left lever was pulled to release the pressure. It's possible to tell them apart now that the discs have been removed. It looked like a nice, clear film that was acquired.

Once the sample has been taped to the IR sample holder with Scotch tape, the spectral analysis can begin. Drug mixture preparations were made using a 1:1 ratio, and the resulting solids were sieved using a No. 30 mesh screen. We prepared the vials by placing drug and excipient samples inside, capping them, and labelling them. Next, the vials were stored at 4 degrees Celsius or 40 degrees Celsius with 75% relative humidity. All combinations were checked on days 0-7, 15-30. Compatibity between drugs and excipients was studied using X-ray diffraction and Fourier transform infrared spectroscopy. The researchers looked at the tablets and capsules that the drugs come in.

Experimental Methods:

Scanning of λ_{max} of Pranlukast:

Preparation of Stock Solution: Pranlukast (10 mg) was withdrawn into a 10 ml volumetric flask. The drug was dissolved by adding 2 ml of methanol and shaking the mixture thoroughly. The final concentration was 1000 g/ml, and it was achieved by diluting the solution with a 6.8pH buffer.

Take 1 millilitre of the above mixture and dilute it to 10 millilitres in a 6.8 pH buffer to get a 100 milligrams per millilitre concentration. Dilution of 1 millilitre of the above solution to 10 millilitres in a 6.8 pH buffer will yield a concentration of 10 milligrams per millilitre. The prepared solution (with a concentration of 10 g/ml) was scanned from 200 to 400 nm in a UV/Visible spectrophotometer for maximum absorbance.

Calibration curve of Pranlukast in 6.8pH buffer:

Preparation of stock solution:

Pranlukast (10 mg) was withdrawn into a 10 ml volumetric flask. To the final concentration was 1000 g/ml, and it was achieved by diluting the solution with a 6.8pH buffer. One millilitre of the aforementioned solution, adjusted to a 6.8pH buffer to yield 100 g/ml concentration, should be used.

Concentrations of 5, 10, 15, 20, 25, and 30 g / ml were obtained by diluting the above stock solution with 6.8pH buffer solution. Volumes of 0.5, 1, 1.5, 2, 2.5, and 3 ml were used. At max, or 246 nm, of Pranlukast in UV/Visible spectroscopy, the absorbance of each test solution was determined in comparison to a blank.

PRANLUKAST SOLID DISPERSION PREPARATION:

It has been reported that both PEG 4000 and PEG 6000 are useful carriers for the preparation of solid dispersions via solvent evaporation.

Solvent evaporation method:

Prior to evaporation, Methanol mixtures of the drug and carriers at 1:0.25 and 1:0.5 were prepared. To get rid of the solvent, low pressure evaporation was used. The material was ground until it could fit through a No. 100 sieve. A desiccator was used to keep the obtained product dry.

T**able 1: Pranlukast Solid Dispersion Formulation with Polyethylene Glycol 4000**

Formulation code	**Drug: polymer**	**Drug : polymer ratio**
F1	Pranlukast: PEG 4000	1:0.25
F2		1:0.5

Table 2: Pranlukast Solid Dispersion Formulation with Polyethylene Glycol 6000.

Formulation code	**Drug: polymer**	**Drug : polymer ratio**
F3	Pranlukast: PEG 6000	1:0.25
F4		1:0.5

FORMULATION OF PRANLUKAST TABLETS:

The table below details the formulas used to formulate the tablets by direct compression using an equivalent weight of Pranlukast and suitable excipients.

Before being added, each ingredient was strained through a #60 sieve. Small amounts of the drug and Mannitol were mixed together to form a paste, and then set aside. After adding the final ingredients and giving the mixture a good stir, the tablets were pressed using a hydraulic press after being strained through a coarse sieve (#44 mesh). Through tinkering with the compression

force of the machine, we were able to achieve a consistent hardness of between 3 and 4 kg/cm2 across all runs. Weight was consistent across all six tablet formulations (F1–F6).

Table 3: Disintegrating Pranlukast Tablets Formulation

INGREDIENTS	F1	F2	F3	F4	F5	F6
Pranlukast S.D Wt. equivalent(mg)	292.95	292.95	292.95	292.95	292.95	292.95
Crospovidones (mg)	5	10	15	-	-	-
Crosscarmellose Sodium (mg)	-	-	-	5	10	15
MCC(mg)	96.05	91.05	86.05	96.05	91.05	86.05
Magnesium Stearate(%)	3.1	3.1	3.1	3.1	3.1	3.1
Talc(%)	2.9	2.9	2.9	2.9	2.9	2.9
TOTAL(mg)	400	400	400	400	400	400

RESULTS & DISCUSSION

PREFORMULATION STUDIES

Determination of melting point

The melting point of Pranlukast was determined by capillary method to be 237° C.

Solubility

Pranlukast solubility was tested at 250°C using 0.1 N HCL, 6.8 phosphate buffer, and purified water.

Table :4 Solubility Studies of Pranlukast

MEDIUM	SOLUBILITY(mg/ml)
water	0.056
0.1 N HCL	0.205
6.8 PH buffer	0.584

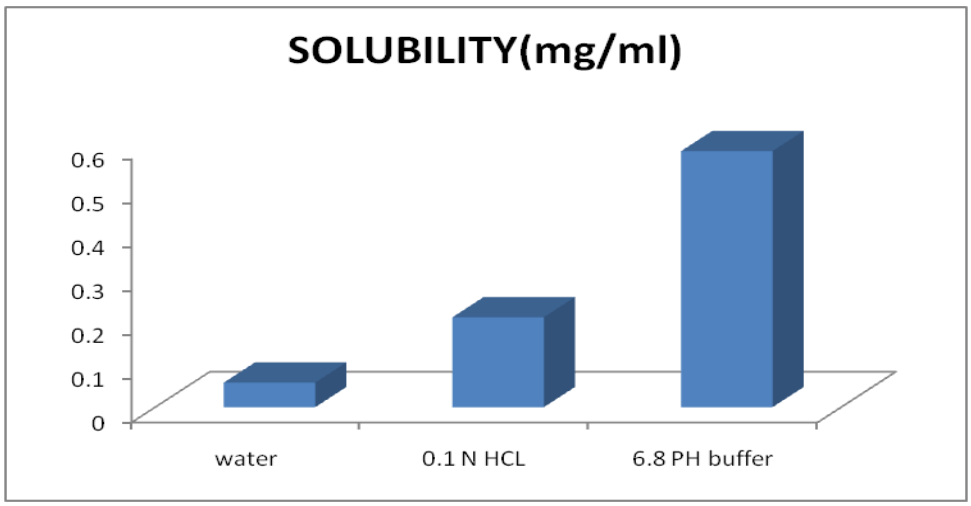

Fig 1: Solubility studies of Pranlukast

Discussion: Solubility studies in various buffers led researchers to conclude that a 6.8pH buffer solution offers the best solubility conditions.

UV spectroscopy as a tool for developing analytical methods:

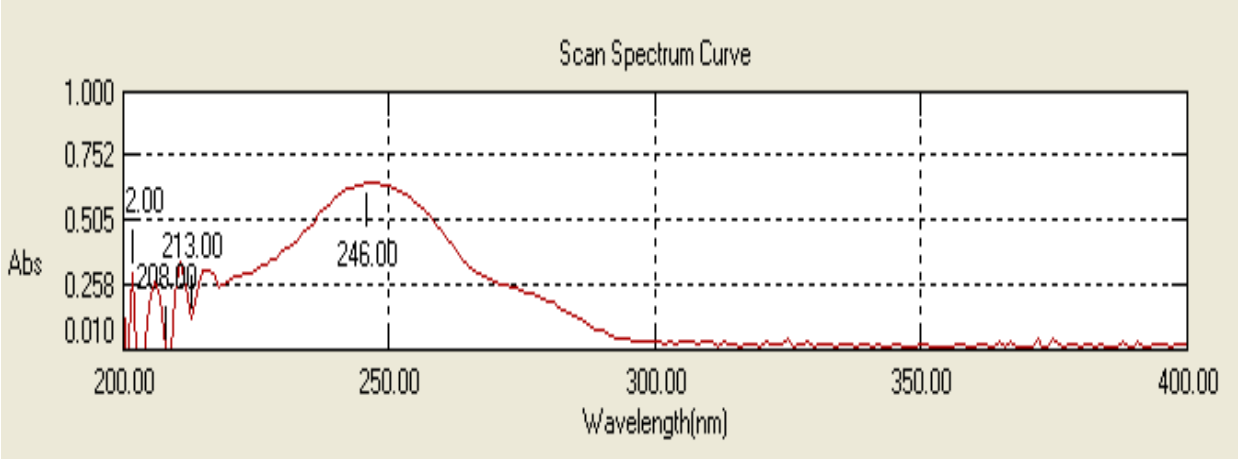

Fig 7.2: Pranlukast UV Absorption Spectral Linewidth

Calibration Curve Data of Pranlukast:

Table 5: Calibration Curve Data of Pranlukast

Concentration(µg/ml)	Absorbance
0	0
5	0.131
10	0.236
15	0.342

20	0.456
25	0.575
30	0.674

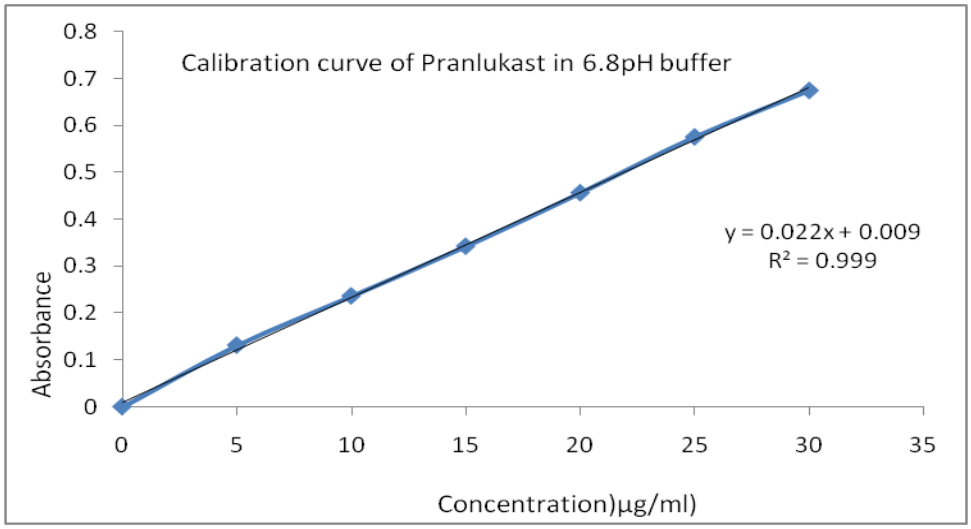

Fig 3: Calibration curve of Pranlukast

Drug excipient compatibility: By comparing FT-IR spectra of pure drug with those of various excipients used in the formulation, drug and excipient compatibility was confirmed

.

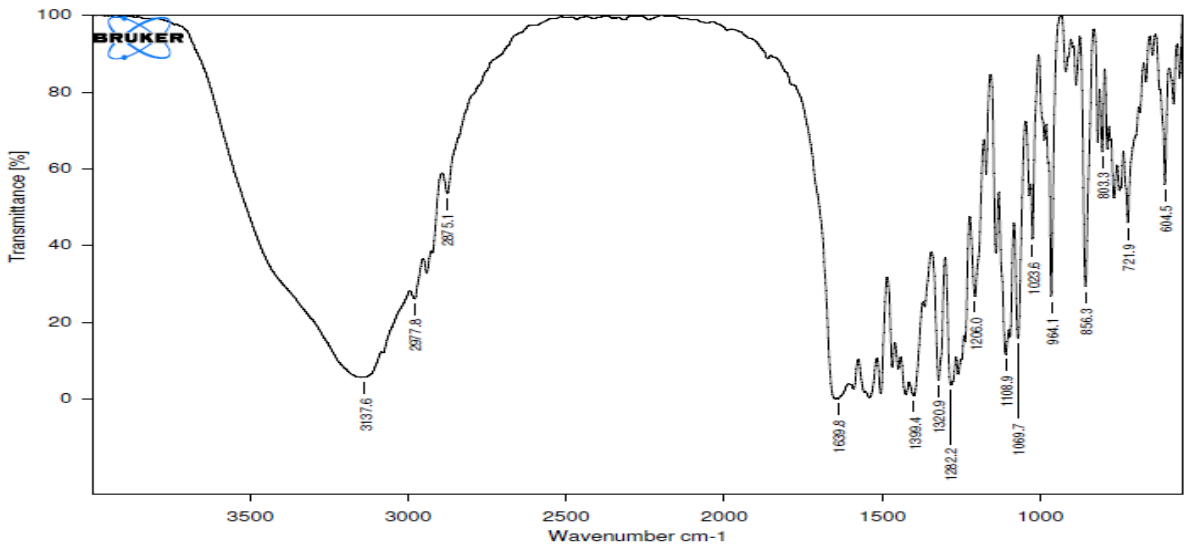

Fig 4 : IR spectrum of pure Pranlukast

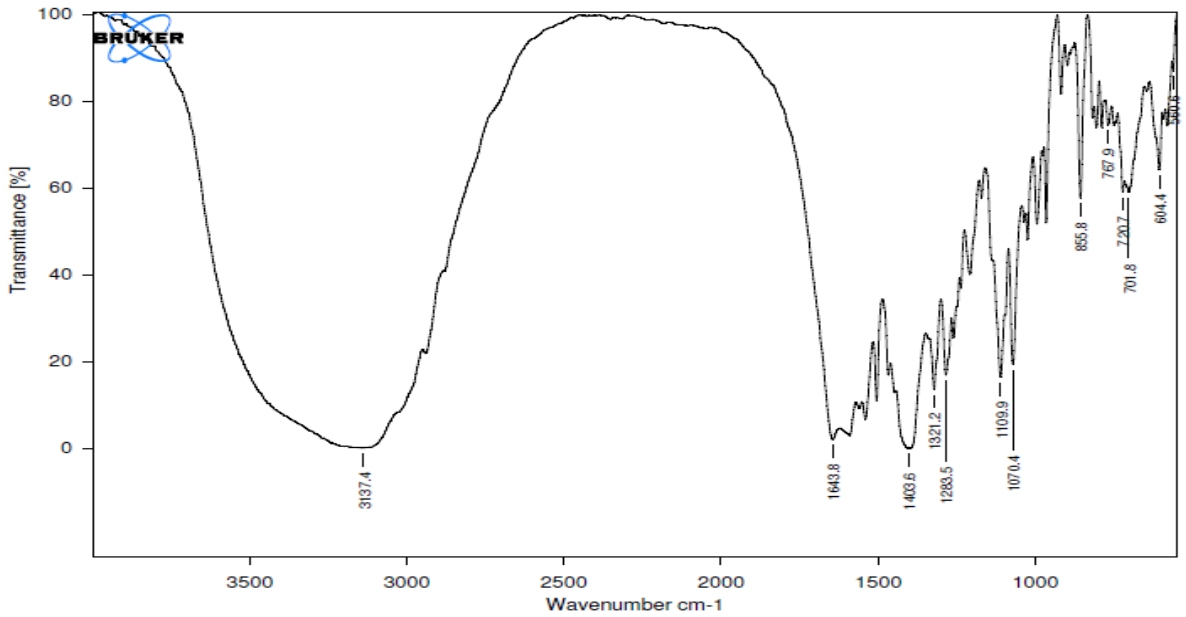

Fig 5 : IR spectrum of Pranlukast Optimised Formulation

Discussion: Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Pranlukast) and optimized formulation (Pranlukast: excipients) which indicates there are no physical changes.

Table 6: Solid dispersions' uniformity in drug content and percentage yield from solvent evaporation

Formulation code	Percentage yield(%)	%Drug content
F1	66.72±0.94	69.64±0.34
F2	73.46±0.26	76.21±0.29
F3	84.16±0.58	85.82±0.54
F4	86.80±0.22	89.76±0.33

Invitro drug release studies of solid dispersions:

Table 7: Invitro drug release studies of Pranlukast solid dispersions for formulations (F1-F4)

S.No	Time (Min)	Percentage drug release			
		1:0.25 (F1)	1:0.5(F2)	1:0.25(F3)	1:0.5 (F4)
0	0	0	0	0	0
1	5	32.78±0.59	35.12±0.48	19.26±0.14	22.86±0.51

2	10	39.92±0.33	39.98±0.62	31.22±0.22	39.85±0.20
3	15	47.36±0.14	49.82±0.22	42.82±0.36	48.28±0.04
4	20	56.28±0.25	58.22±0.41	51.21±0.98	62.48±0.69
5	30	64.86±0.84	74.86±0.20	68.36±0.42	74.21±0.48
6	45	74.16±0.52	78.21±0.08	78.16±0.57	82.96±0.22

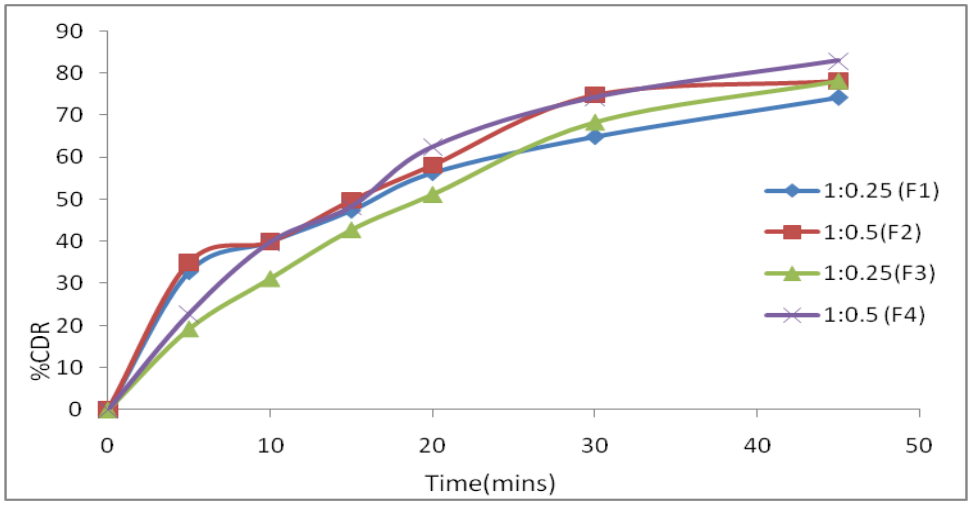

Fig 6 : *Invitro* drug release profile of solid dispersions for (F1-F2) & (F3-F4)

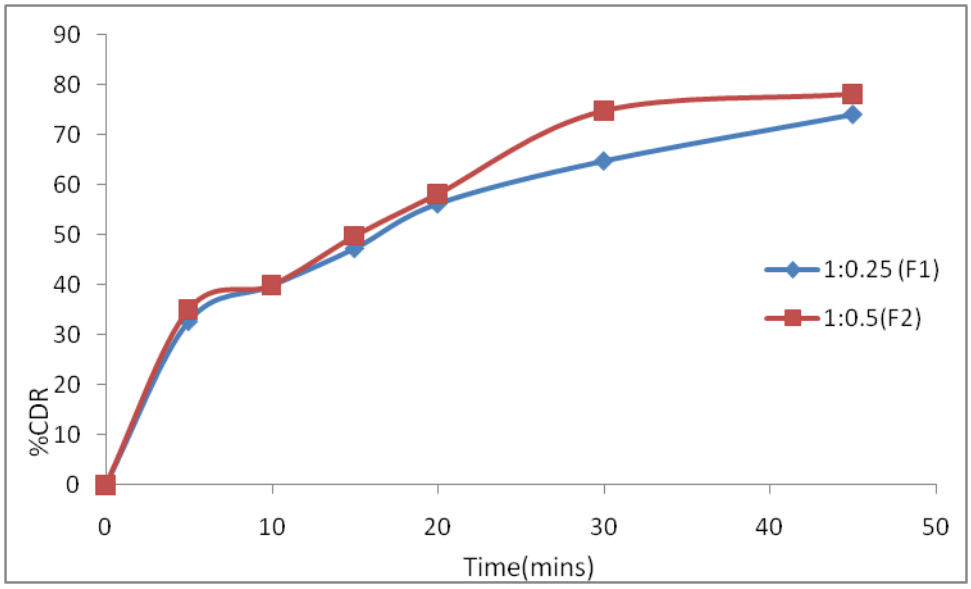

Fig 7 : *Invitro* drug release profile of solid dispersions for (F1-F2)

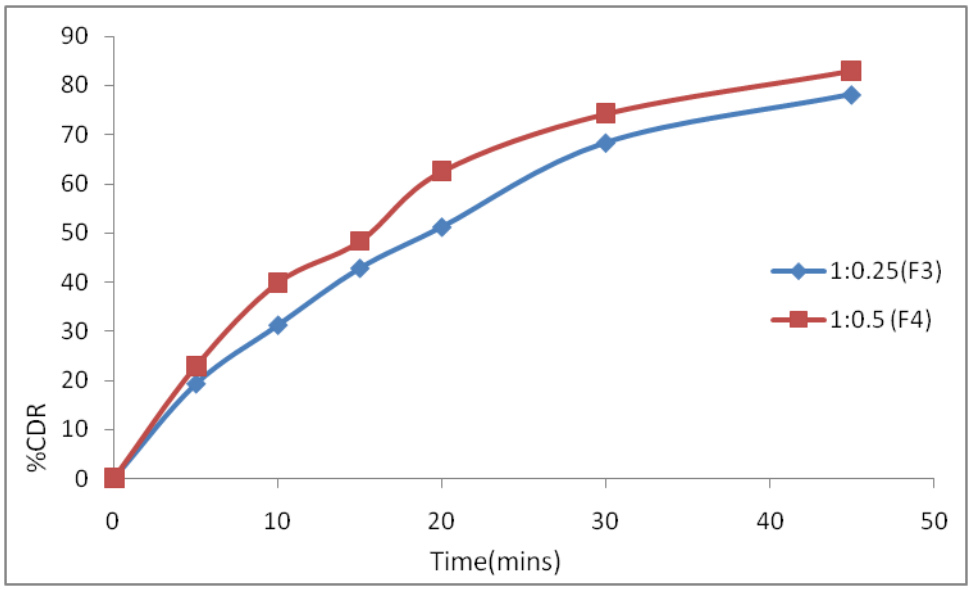

Fig 8 : *Invitro* drug release profile of solid dispersions for (F3-F4)

DISCUSSION: *Invitro* drug release of Pranlukast solid dispersions with PEG 4000 and PEG 6000 in various ratios were observed which shows at the end of 45 mins the formulation F1 releases 74.16±0.52, formulation F2 releases 78.21±0.08, formulation F3 releases 78.16±0.57, formulation F4 releases 82.96±0.22%.

Evaluation of tablets:

Pre Compression parameters of Pranlukast oral disintegrating tablets:

When compared across formulations, the angle of repose was 30.68 degrees, indicating a high degree of fluidity. The blends' free-flowing nature was thus verified. Blend was found to have a bulk density of between 0.42g/cm3 and 0.52g/cm3. It was determined that the density ranged from 0.48g/cm3 to 0.60g/cm3 after being probed. These numbers suggest that the mixtures' flow properties were satisfactory. The blends have good flow character, as evidenced by the Carr's index values (ranging from 11.53 to 15.518) and the Hausner's ratio values (between 1.12 and 1.18). **Post Compression parameters of Pranlukast oral disintegrating tablets:**

The tablet's hardness, measured at a range of 3.68 to 4.28 kg/cm2, was found to be suitable and consistent from batch to batch. The percent weight variation of all the formulations was within the pharmacopoeial limits of the tablet weight, so they all passed the weight variation test. All six formulations (F1–F6) were found to have friability values of less than 1%, which is considered satisfactory and guarantees that they are mechanically stable.

Discussion: The percentages of drug content in formulations F1 (95.96%), F2 (97.65%), F3 (99.62%), F4 (98.02%), F5 (98.71%), and F6 (98.16%) are as follows. All of the formulations (F1-F6) had drug contents between 95.96 and 99.62 percent.

Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table 8 : In vitro drug release of Pranlukast oral disintegrating tablets formulations F1-F6

Time(Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	24.22±0.62	26.42±0.14	34.26±0.24	19.84±0.22	26.22±0.04	31.26±0.10
10	33.81±0.14	38.77±0.28	41.65±0.26	32.54±0.48	36.41±0.12	38.38±0.28
15	46.29±0.22	50.28±0.69	54.17±0.58	45.30±0.68	48.71±0.63	50.85±0.34
20	60.80±0.48	66.48±0.20	71.31±0.64	58.12±0.24	63.64±0.24	68.23±0.19
30	72.25±0.26	81.85±0.48	89.46±0.23	75.23±0.29	79.84±0.58	85.53±0.24
45	91.87±0.24	97.17±0.10	96.74±0.14	89.78±0.84	93.59±0.48	98.02±0.34

IN VITRO DRUG RELEASE OF OF PRANLUKAST ORAL DISINTEGRATING TABLETS F1-F6:

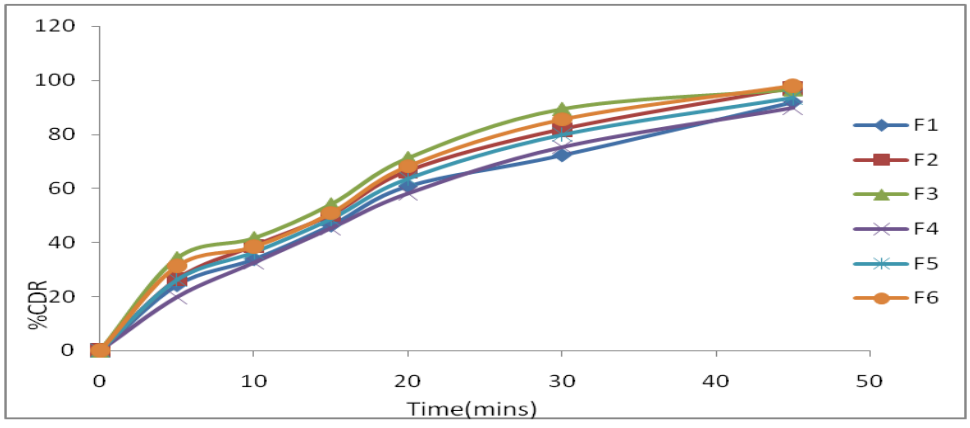

Fig 9 : In vitro drug release of oral disintegrating tablets formulations F1-F6

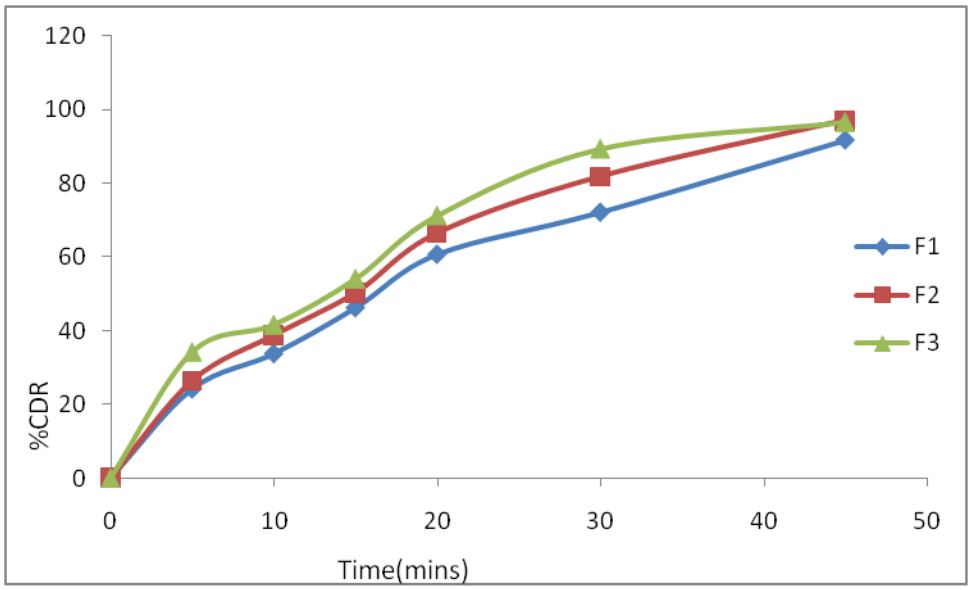

Fig 10 : In vitro drug release of oral disintegrating tablets formulations F1-F3

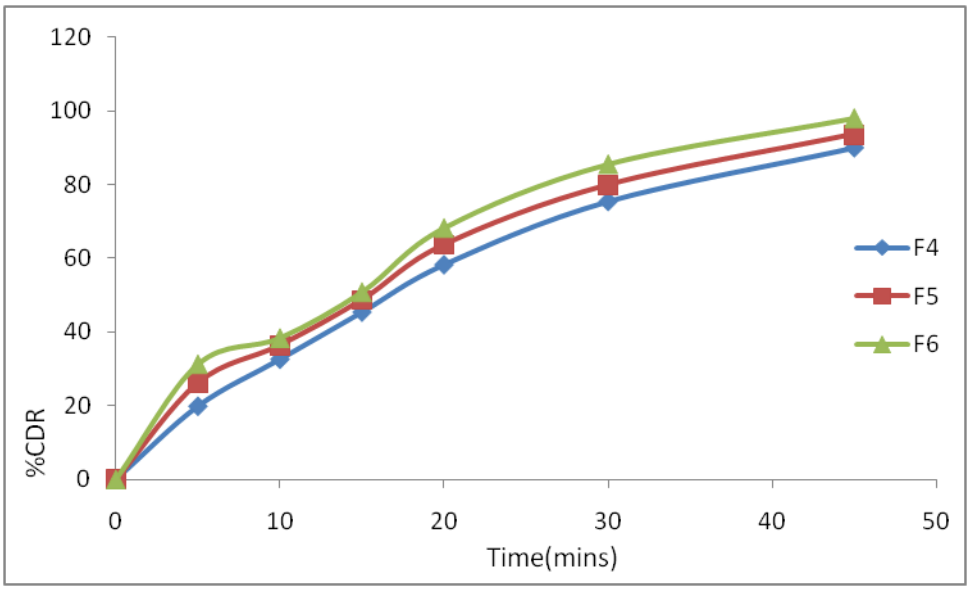

Fig 11 : In vitro drug release of oral disintegrating tablets formulations F4-F6

Discussion:

In vitro drug release studies on formulations containing Crospovidones as a super disintegrants at various concentrations (five, ten, and fifteen milligram) show that increasing the super disintegrants concentration decreases the drug release time, with the highest amount of drug release (96.74 percent) occurring after 45 minutes in the F3 formulation. In contrast, studies of formulations containing Crosscarmellose Sodium as a super disintegrants at 5, 10, and 15 mg concentrations show that increasing the super disintegrants concentration shortens the drug release time, with the F3 formulation containing Crosscarmellose Sodium 15 mg demonstrating the highest amount of drug release (98.02 percent) after 45 minutes.

DRUG RELEASE KINETICS:

ZERO ORDER PLOT OF (F6):

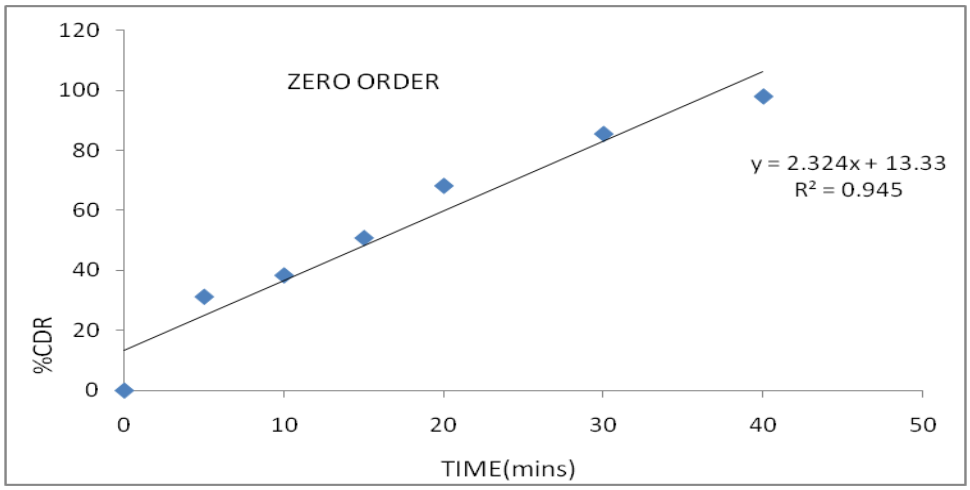

Fig 12: ZERO ORDER PLOT OF (F6)

FIRST ORDER PLOT OF (F6):

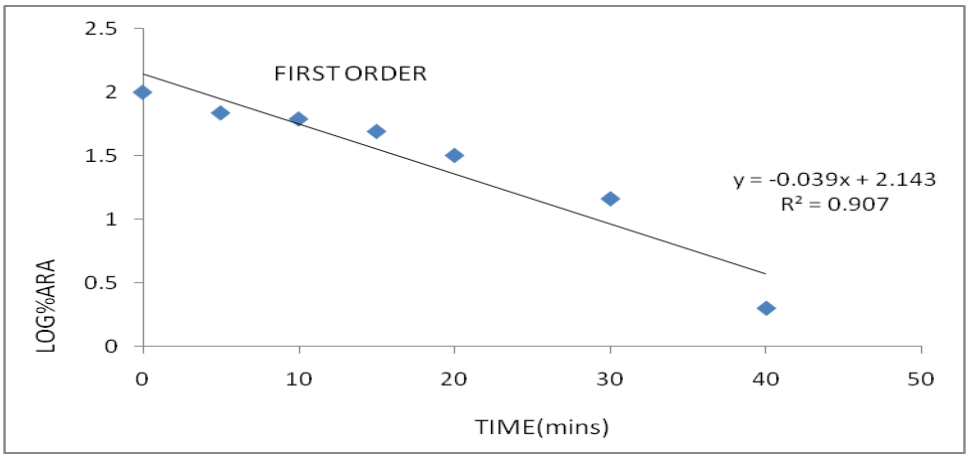

Fig 13: FIRST ORDER PLOT OF (F6)

Table 9: order of kinetic values of FormulationF6:

Order of kinetics	Zero Order	First Order
Regression values	0.945	0.907

Discussion:

Mathematical model equations, including zero order and first order methods, were used to explain how the tablets' drug release would occur. It was determined from the regression values that the optimal formulation F6 exhibits zero order kinetics.

SUMMARY AND CONCLUSSION

In this study, every step of the process from methodology to materials to experiments was described in detail. Afterwards, we covered how to make a Pranlukast physical mixture or solid dispersion by evaporating the solvent. Different carriers were used to create solid dispersions of pranlukast with varying drug-to-carrier ratios (1:0.25, and 1:0.5). Pranlukast solid dispersions were prepared using the solvent evaporation method, and the entrapment efficiency, melting point, drug content uniformity, and in vitro dissolution were all discussed.

Many different types of analysis, including FT-IR, were applied to the solid state. Final comparisons between all four formulations (SF1-SF4) showed that SF4, containing Pranlukast+ PEG 6000 (1:0.5), provided the best results by solvent evaporation method at the end of 90 minutes, with drug release of 82.96 percent. In vitro drug release testing was performed on the finished tablet formulation in a 6.8pH buffer. Crosscarmellose Sodium (7.5mg)-enhanced F6 formulations have been shown to achieve 98.02 percent drug release within 40 minutes. A zero-order model of release kinetics is used in the optimal formulation.

REFERENCE

1. Noyes, A.A., and Whitney W.R., (1897). The rate of solution of solid substances in their own solutions, *J. Am. Chem. Soc*., 19: 930-934.

2. Van Drooge, D.J. et al. (2006). Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm,*. 310: 220–229.

3. Galia, E., Nicolaides, E., HoÈrter, D., LoÈbenberg, R., Reppas, C., and Dressman, J.B., (1998). Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm. Res*., 15: 698-705.

4. Sengodan guruswamy, V., and Mishra, D.N., 2006. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. *The Pharmaceutic. Soc. Jap.,* 126(2): 93-97.

5. Hancock, B.C., and Zogra, G., (1997). Characteristics and significance of the amorphous state in pharmaceutical systems (review). *J. Pharm. Sci.,* 86: 1-12.

6. Hoerter, D., and Dressman, J.B., (1997). Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract (review). *Adv. Drug Delivery Rev.*, 25-14.

7. Loftsson, T., and Brewster, M.E., (1996). Pharmaceutical application of cyclodextrins. 1. Drug solubilisation and stabilization (review). *J. Pharm. Sci.,* 85: 1010-1025.

8. Sekiguchi, K., and Obi, N., (1961). Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.,* 9: 866-872.

9. Taylor, L.S., and Zogra, G., (1997). Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.,* 14: 1691-1698.

10. Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II ± experimental evaluation of a eutectic mixture: urea±acetaminophen system. *J. Pharm. Sci*., 55: 482-487.

11. Chiou, W.L., and Rielman, S., (1971). Pharmaceutical application of solid dispersion system. *J.Pharm.Sci.,* 60: 1281-1302.

12. Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1965). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I theoretical considerations and discussion of the literature. *J. Pharm. Sci.,* 54: 1145-1148.

13. Kreuter, J., Kreuter, J., and Herzfeldt, C.D., (1999). Grundlagen der Arznei-formenlehre Galenik, 2, Springer, Frankfurt am Main. 262-274.

14. Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.,* 58: 1505-1510.

15. Vasconcelos, T.F., Sarmento, B., and Costa, P., (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug discovery today*., 12: 1069-1070.

6. Sekiguchi, K., and Obi, N., (1964). Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. *Chem. Pharm. Bull.,* 12: 134–144

17. Sekiguchi, K. and Obi, N., (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.,* 9: 866–872.

18. Levy, G., (1963). Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. *Am. J. Pharm. Sci.,* 135: 78–92.

19. Kaning, J.L., (1964). Properties of Fused Mannitol in Compressed Tablets. *J. Pharm. Sci.,* 53: 188– 192.

20. Goldberg, A.H., et al. (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol– urea system. *J. Pharm. Sci.,* 55: 581–583.

21. Simonelli, A.P., et al. (1969). Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. *J. Pharm. Sci.*, 58:

538–549.

22. Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58: 1505–1510.

23. Urbanetz, N.A., (2006). Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. *Eur. J. Pharm. Sci.*, 28: 67–76.

24. Vilhelmsen, T., et al. (2005). Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J. Pharm.*, 303: 132–142.

25. Goldberg, A., Gibaldi, M., and Kanig, L., 1996. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system, *J. Pharmaceut.Sci.,* 55: 482-487.

26. Serajuddin, A., 1999. Solid dispersion technique. *J. Pharmaceut. Sci.,* 88 (10): 891-900.

27. Narang, A., and Shrivastava, A., 2002. Melt extrusion solid dispersion technique. *Drug Dev. Ind. Pharm.*, 26(8): 111-115.