

FORMULATION AND EVALUATION OF RESPERIDONE ORAL FILM

Sonali Shrimant Karnor¹ , Dr.Sunil Nirmal² Dr.Jaydeep Pawar, Rajiya Khan¹ ,

¹ Hon. Shri. Babanrao Pachpute Vichardhara Trust Group of Institutions, Faculty of Pharmacy, Kashti.

Co Author: Sonali Shrimant Karnor

Co Author: Dr.Sunil Nirmal

Co Author: Rajiya Khan

Corresponding Author: Dr.Jaydeep Pawar

ABSTRACT:

The oral route is highly favored for drug administration due to its ease of use, painlessness, versatility, and high patient compliance. Orally disintegrating films, offer a promising alternative, particularly benefiting patients with swallowing difficulties like the elderly and children. This study focuses on the development and evaluation of risperidone orally disintegrating films, using hydrophilic polymers HPMC E15CPS, HPMC E15, and HPMC E5. The films were assessed for visual and tactile properties, thickness, weight uniformity, folding endurance, drug content uniformity, surface Ph, disintegration time, and in-vitro drug release. The films exhibited a smooth, elegant surface, thicknesses from 0.234 mm to 0.271 mm, and weight variations within $\pm 10\%$. Folding endurance ranged from 38 ± 1 to 57 ± 2 folds, with neutral surface pH. Drug content uniformity was between 98% and 102%, and disintegration times ranged from 21 to 32 seconds. Batch F-9, with an in-vitro disintegration time of less than 27 seconds, displayed optimal mechanical properties and drug release profile, making it the most suitable formulation. Stability studies confirmed the integrity of the formulation over time. Thus, risperidone orally disintegrating films present a viable, patient-friendly option for improved drug delivery.

Keywords: Risperidone, Fast-dissolving drug delivery, Hydrophilic polymers, HPMC E15CPS, HPMC E15, HPMC E5

INTRODUCTION:

The oral route^{1,2} of administration is highly favored due to its ease of use, painlessness, versatility, and high patient compliance. Fast-dissolving drug delivery systems, such as oral strips, are becoming popular for their easy administration and enhanced patient adherence. These thin films, composed of hydrophilic polymers, dissolve rapidly in the mouth without water, making them suitable for individuals with swallowing difficulties, including approximately 35-50% of the population such as the elderly and children.

Patients with dysphagia, young individuals with underdeveloped systems, those with tremors, mental illness, or limited liquid intake, and those experiencing motion sickness or allergic attacks benefit greatly from these films. Traditional pills and capsules pose choking risks, particularly for pediatric and geriatric patients. While orally disintegrating tablets (ODTs) dissolve in the mouth, the risk of choking remains. Fast-dissolving films, however, dissolve completely, eliminating these concerns.

Oral bioavailability of many drugs is often compromised by stomach pH, enzymes, and extensive first-pass metabolism, traditionally necessitating parenteral administration, which lowers patient compliance. **Fast-dissolving films (FDFs)** are an innovative drug delivery system designed to enhance solubility, stability, and bioavailability of drugs. These films dissolve rapidly when placed on the tongue, allowing for quick release of the active agent, which can then be absorbed either locally or systemically.

In summary, fast-dissolving films provide a promising alternative to traditional oral dosage forms, particularly benefiting patients with swallowing difficulties. They enhance compliance and address the limitations of conventional oral dosage forms, presenting a patient-friendly and effective drug delivery option.

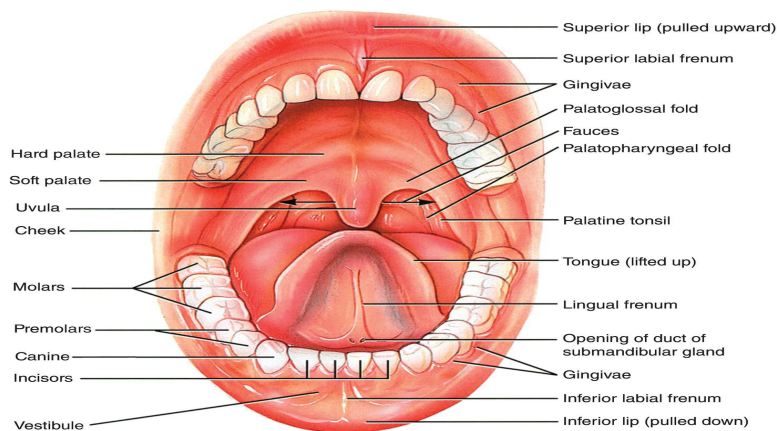


Fig.1 Structure of Oral cavity

DRUG PROFILE

RISPERIDONE

Risperidone³, “a benzisoxazole derivative, is an atypical antipsychotic with high affinity for 5-HT and dopamine D2 receptors. It is primarily used to manage schizophrenia, inappropriate behavior in severe dementia, and manic episodes in bipolar I disorder. Risperidone treats both positive and negative symptoms of schizophrenia due to its "loose" binding to D2 receptors and additional 5-HT antagonism, unlike first-generation antipsychotics which are strong, non-specific D2 antagonists”.

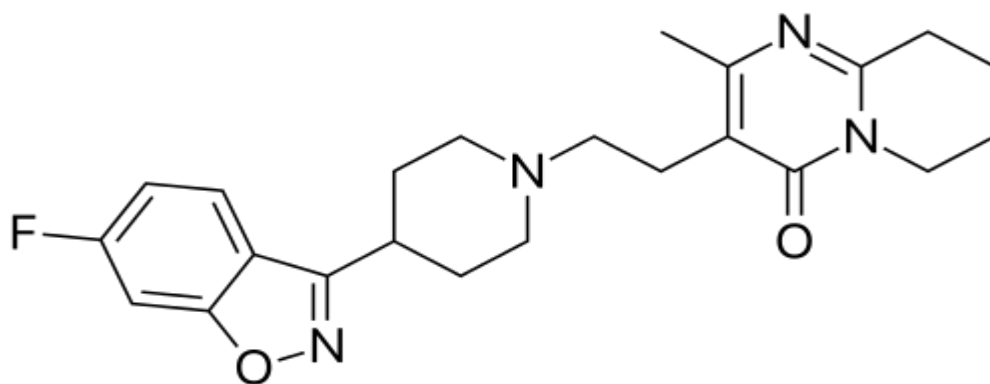


Fig 2 : Structure of Risperidone

MATERIALS AND METHODS

After weeks of drug excipient compatibility testing, the below excipients was selected for the formulation.

Risperidone was sourced from Pharmatrain in Hyderabad. ‘HPMC E15, HPMC E5, propylene glycol, sorbitol, aspartame, Tween 80, citric acid’ and the flavoring agent were all procured from S.D. Fine Chemicals in Mumbai

METHODOLOGY

1. Analytical Method Development



Fig 5: UV-VIS Spectrophotometer 3000+

Preparation of 6.8 Phosphate Buffer: ‘Dissolve 6.8 g of potassium dihydrogen ortho phosphate in distilled water in a 1000 ml volumetric flask, then make up to 1000 ml with distilled water. Adjust the pH to 6.8 with sodium hydroxide solution.’

Determining the Risperidone λ_{\max} in “6.8 Phosphate Buffer Procedure”: ‘Dissolve 50 mg of Risperidone in 50 ml of 6.8 phosphate buffer to make a 1000 $\mu\text{g}/\text{ml}$ stock solution. Dilute 10 ml of this solution to 100 ml with buffer to make a 100 $\mu\text{g}/\text{ml}$ solution. Further dilute 10 ml of this to 100 ml with buffer for a 10 $\mu\text{g}/\text{ml}$ solution.’ Scan this solution from 200-400 nm and note the wavelength with the highest absorbance (λ_{\max}).

Construction of Risperidone Calibration Curve in 6.8 Phosphate Buffer: Dissolve 50 mg of Risperidone in 50 ml buffer to create a 1000 $\mu\text{g}/\text{ml}$ stock solution. ‘Dilute 10 ml of this to 100 ml’ to get a 100 $\mu\text{g}/\text{ml}$ solution. From this, take 0.5, 1, 1.5, 2, and 2.5 ml, and dilute each to 10 ml to obtain 5, 10, 15, 20, and 25 $\mu\text{g}/\text{ml}$ solutions. Measure the absorbance at $\lambda_{\max} = 280 \text{ nm}$.

Solubility Determination: Add excess Risperidone to 25 ml of water, shake for 24 hr, then filter and dilute. Measure absorbance using a UV-spectrophotometer to determine solubility.

Photostability Studies: Mix the drug with excipients in a 1:1 ratio and expose to sunlight for 1 month in 10 ml glass vials.

Fourier Transform Infrared Radiation: Analyze pure drug, pure polymer, and their physical mixture using FTIR from 4000 cm^{-1} to 400 cm^{-1} with the KBr pellet method for interaction studies.

Formulation of Risperidone Disintegrating Films:

Preparation by Solvent Casting Method: Prepare an aqueous polymer solution and add Risperidone. Add propylene glycol, aspartame, and peppermint flavor. Cast the solution on a petri dish, dry for 24 hr, remove the film, and cut into 2x2 cm strips. Store in a desiccator.

Formulation of Fast Dissolving Films: In 5 ml of water, the HPMC-E15 polymer was dissolved to make Solution 'A'. In 5 ml of ethanol, risperidone, aspartam, sorbitol, and citric acid were dissolved to create Solution 'B'. Mix Solutions A and B, stir for 30 min, add propylene glycol, Tween 80, and flavoring agent, and stir for 10 min. Cast onto a 9 cm diameter petri plate, dry at 70°C , and cut into 2x2 cm pieces containing 10 mg Risperidone per 4 cm^2 film.

Table no. 2. Formulation of Risperidone fast disintegrating films

“Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Risperidone	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC E15	25	30	35	40	45	50	10	20	30
HPMC E5	-	-	-	-	-	-	30	20	10
Propylene glycol	10	10	10	10	10	10	10	10	10
Sorbitol	34	29	24	19	14	9	19	19	19
Aspartame	5	5	5	5	5	5	5	5	5
Tween 80	5	5	5	5	5	5	5	5	5
Saliva stimulating agent (citric acid)	5	5	5	5	5	5	5	5	5
Flavoring agent	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total wt. (mg)	85	85	85	85	85	85	85	85	85”

Calculation:

- **Diameter of Petridish:** 9 cm
- **Radius:** 4.5 cm (9/2)
- **Area:** $\pi r^2 = 3.14 \times 4.5 \times 4.5 = 63.59 \text{ cm}^2$
- **Dose Calculation:** 4 cm² contains 0.5 mg drug, so 63.59 cm² contains 7.95 mg drug.

Evaluation of Risperidone Oral Disintegrating Films:

1. **Weight Uniformity:** Weigh three 2 cm × 2 cm films and calculate the average weight.'
2. **Morphological Properties:** Inspect films visually and evaluate texture by touch.
3. **Thickness Uniformity:** Measure the thickness of films at three spots using a calibrated Vernier caliper and calculate the average.
4. **Folding Endurance:** Fold a 2 cm × 2 cm strip repeatedly until it breaks; note the number of folds.
5. **Surface pH:** Place the film on 1 ml distilled water, bring pH paper to the surface, and note the color change.
6. **Drug Content Uniformity Test:** Dissolve strips equivalent to 2 mg drug in 50 ml 6.8 pH phosphate buffer, filter, dilute to 100 ml, and analyze by UV spectrophotometry at 280 nm.
7. **In Vitro Disintegration Test:** Place the film in 25 ml distilled water, swirl every 10 sec, and note the disintegration time.
8. **In Vitro Dissolution Studies:** Use a paddle dissolution apparatus with '900 ml of 6.8 pH phosphate buffer at $37 \pm 0.5^\circ\text{C}$ and 50 rpm.' Withdraw samples at intervals, replace with fresh medium, and analyze drug release spectrophotometrically at 280 nm. Plot cumulative percent drug release against time.

In Vitro Release Kinetics Studies:

- **'Zero Order Release Kinetics':** $Q = kt$. Plot fraction of drug released vs. time; a linear plot indicates zero order kinetics.
- **'First Order Release Kinetics':** $\text{Log } C = \text{Log } C_0 - kt/2.303$. Plot log cumulative % drug remaining vs. time; a linear plot indicates first order kinetics.'

‘Fourier Transform Infrared (FTIR) Spectroscopy’: Record FTIR spectra of samples prepared in potassium bromide disks using a hydrostatic press. Scan range: 400 to 4000 cm^{-1} , resolution: 4 cm^{-1} . Analyze spectra for drug-carrier interaction.

Stability Studies: Conduct stability studies to determine the inherent stability of the drug, excipient compatibility, and solution phase stability to ensure no toxic substances are formed. Stability studies help avoid or control situations compromising the drug's stability and therapeutic efficiency.

Rationale for Stability Studies:

1. **Chemical Degradation:** ‘Prevent substantial lowering of the therapeutic agent.’
2. **Toxic Product Formation:** Avoid formation of toxic decomposition products.
3. **Therapeutic Efficiency:** Enhance the therapeutic effects of the dosage form.

“Stability Storage Conditions”

Storage stability testing for physical and chemical properties is conducted under different conditions and schedules to assure the integrity of the product over time. For long-term stability, the conditions are $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with $60\% \pm 5\%$ relative humidity (RH), with testing intervals at 3, 6, 9, 12, 18, and 24 months, and then annually until expiry, with an additional check six months post-expiry. Accelerated stability testing is conducted at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with $75\% \pm 5\%$ RH, with evaluations at 1, 2, 3, and 6 months. Intermediate stability testing is carried out at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with $60\% \pm 5\%$ RH, with assessments at 3, 6, 9, and 12 months. For Zone IV stability, the conditions are $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with $70\% \pm 5\%$ RH, with testing scheduled at 3, 6, 9, 12, 18, and 24 months, and annually until expiry, followed by a check six months post-expiry.

RESULTS AND DISCUSSION

“Construction of Standard calibration curve of Risperidone in 6.8 phosphate buffer”:

“The absorbance of the solution was measured at 280nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in the table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer’s law in the concentration range 5 to 25 $\mu\text{g/ml}$.”

Table 3: “Standard Calibration graph values of Risperidone 6.8 phosphate buffer at $\lambda_{\text{Max}} = 280 \text{ nm}$ ”

‘Concentration ($\mu\text{g} / \text{ml}$)’	‘Absorbance’
0	0
5	0.133
10	0.255
15	0.382
20	0.49
25	0.611

“The standard plot of Risperidone is plotted by taking absorbance on Y – axis, and concentration ($\mu\text{g/ml}$) on X – axis, the plot is shown in Fig. No.6”

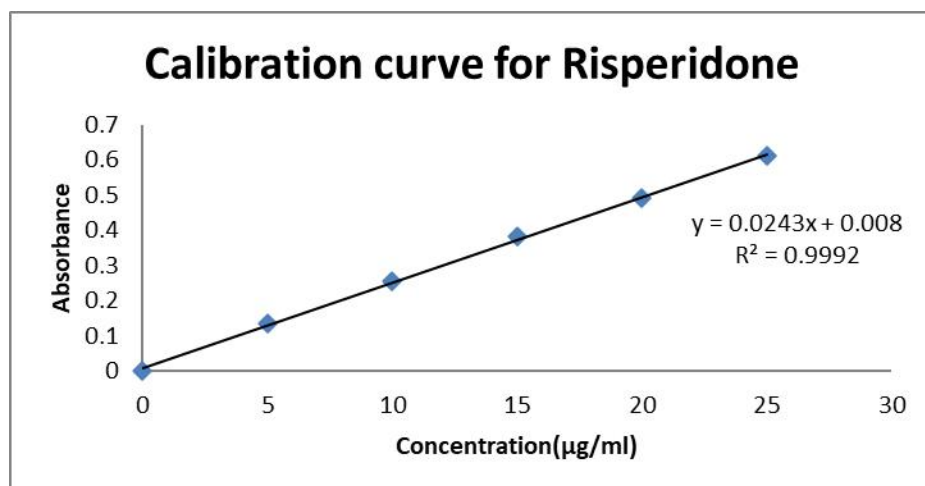


Fig 6: Standard calibration curve of Risperidone in 6.8 phosphate buffer

Inference: The standard calibration curve of Risperidone in 6.8 phosphate buffer showed good correlation with regression value of 0.998.

Table no.4: Evaluation parameters of *Risperidone* FDF

‘Formulation code’	Appearance	‘Thickness (mm)’	‘Weight variation’	‘Folding endurance’	% Assay	Dintegration time(sec)
F1	Smooth and	0.234	87	42	99.13	19

	Transparent					
F2	Smooth and Transparent	0.271	91	51	98.79	24
F3	Smooth and Transparent	0.263	83	38	99.82	21
F4	Smooth and Transparent	0.247	85	57	100.17	27
F5	<i>Smooth and Transparent</i>	<i>0.257</i>	<i>87</i>	<i>54</i>	<i>99.48</i>	<i>32</i>
F6	Smooth and Transparent	0.234	90	49	101.07	28
F7	Smooth and Transparent	0.238	86	45	100.29	26
F8	Smooth and Transparent	0.265	91	39	99.37	23
F9	Smooth and Transparent	0.268	87	48	100.53	27

Inference:

The films were observed to have a smooth and elegant surface. Thickness ranged from 0.234 mm to 0.271 mm, and weights varied within $\pm 10\%$. Folding endurance was between 38 ± 1 and 57 ± 2 folds. Surface pH was neutral, with no color change in litmus paper. Drug content uniformity, measured across three films per trial, was between 98% and 102%. Disintegration time ranged from 21 to 32 seconds.

Table no.5. ‘In-vitro drug release data of formulation F1 to F6’

‘TIME’ (min)	% DRUG RELEASE								
	‘F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0’
3	24	23	35	27	26	24	39	63	65
6	31	35	46	35	39	31	61	76	86
9	38	41	58	49	51	53	83	83	95
12	53	50	72	63	68	68	97	95	100
15	64	59	79	75	80	81	98	99	
18	71	70	85	86	89	95	98		
21	78	82	92	97	97	99			
24	82	89	99	99	100				
27	85	94							
30	91	97							

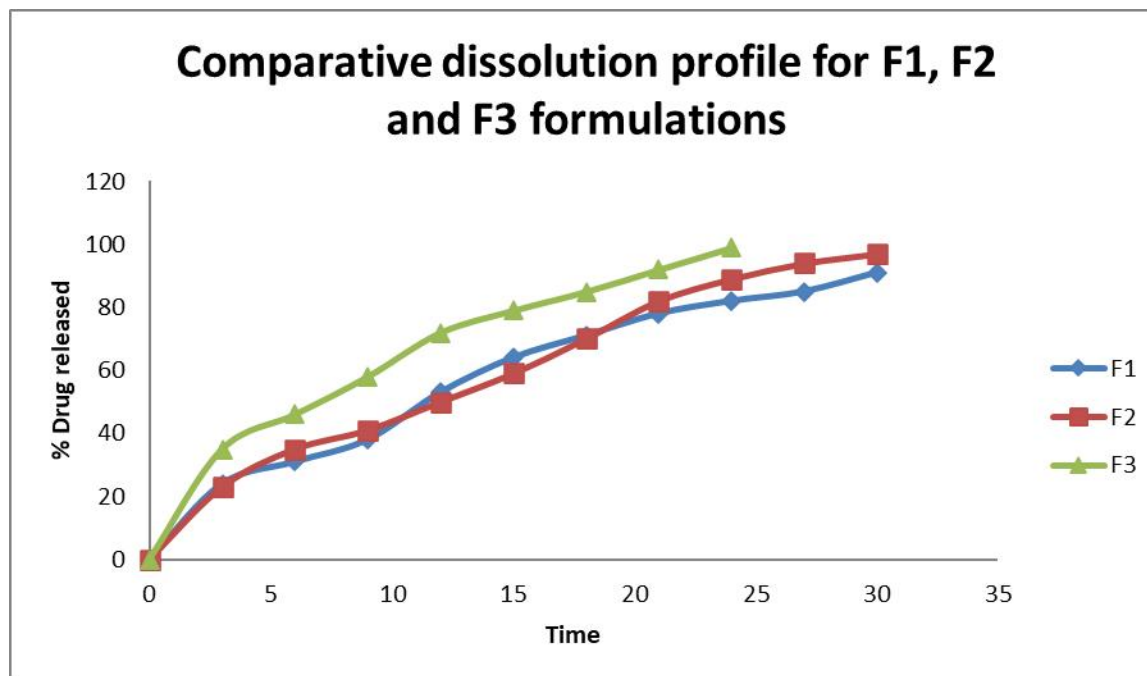


Fig 9: Dissolution profile for F1, F2 and F3 formulations

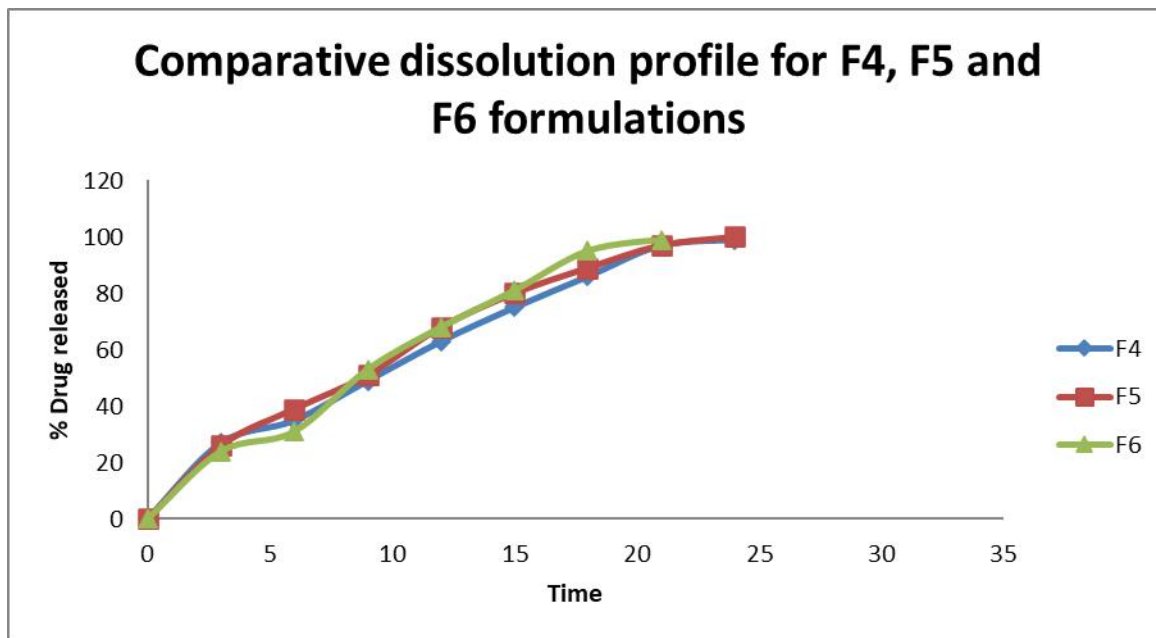


Fig 7: Dissolution profile for F4, F5 and F6 formulations

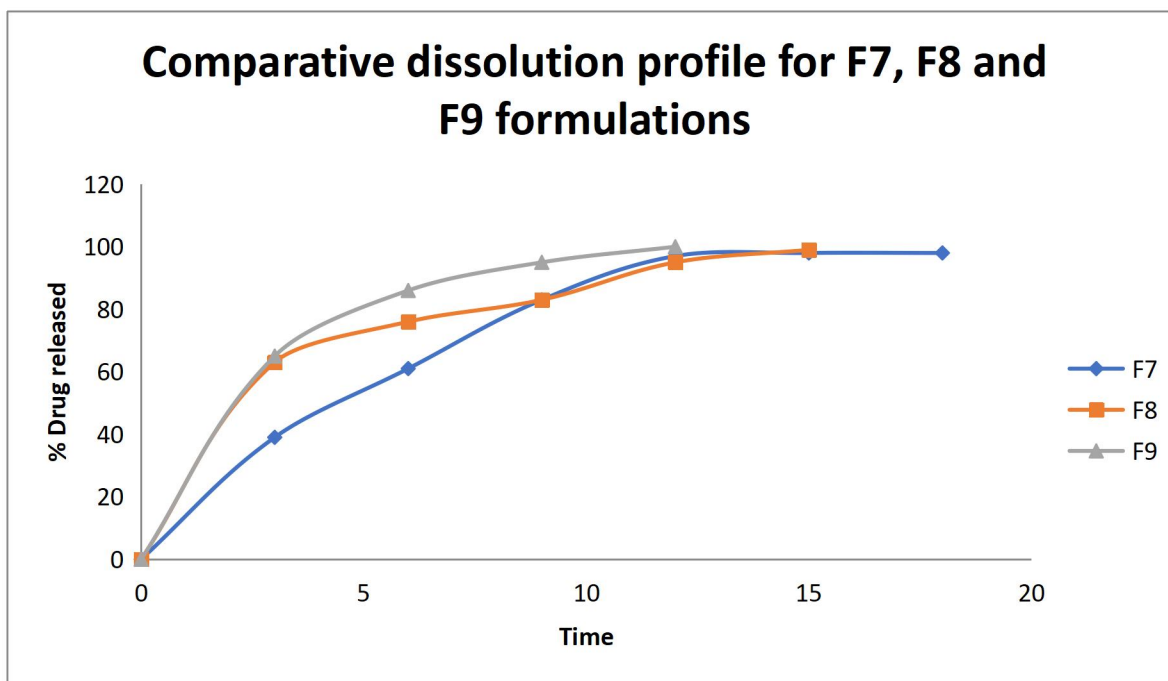


Fig 8: Dissolution profile for F7, F8 and F9 formulations

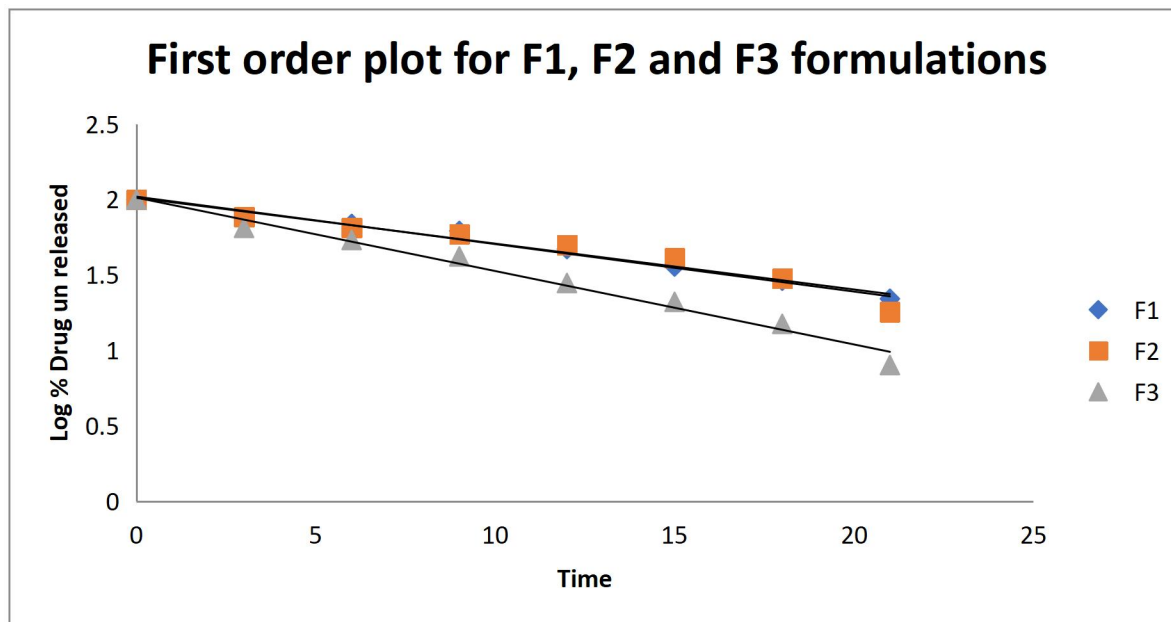


Fig 9: First order plot for F1, F2 and F3 formulations

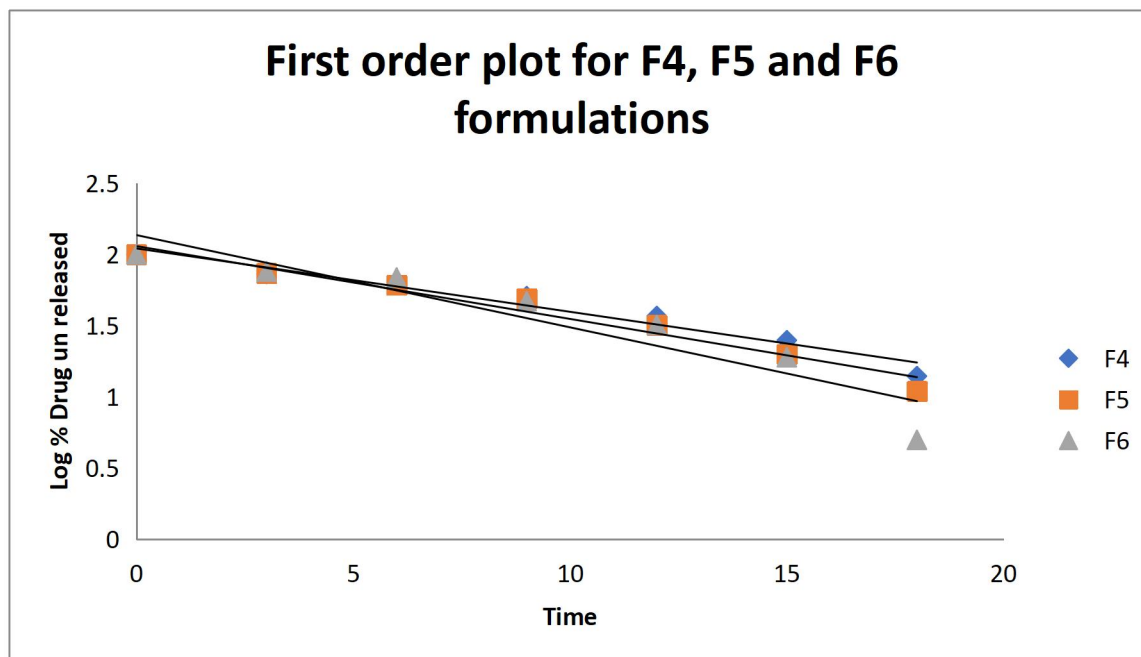


Fig 9: First order plot for F4, F5 and F6 formulations

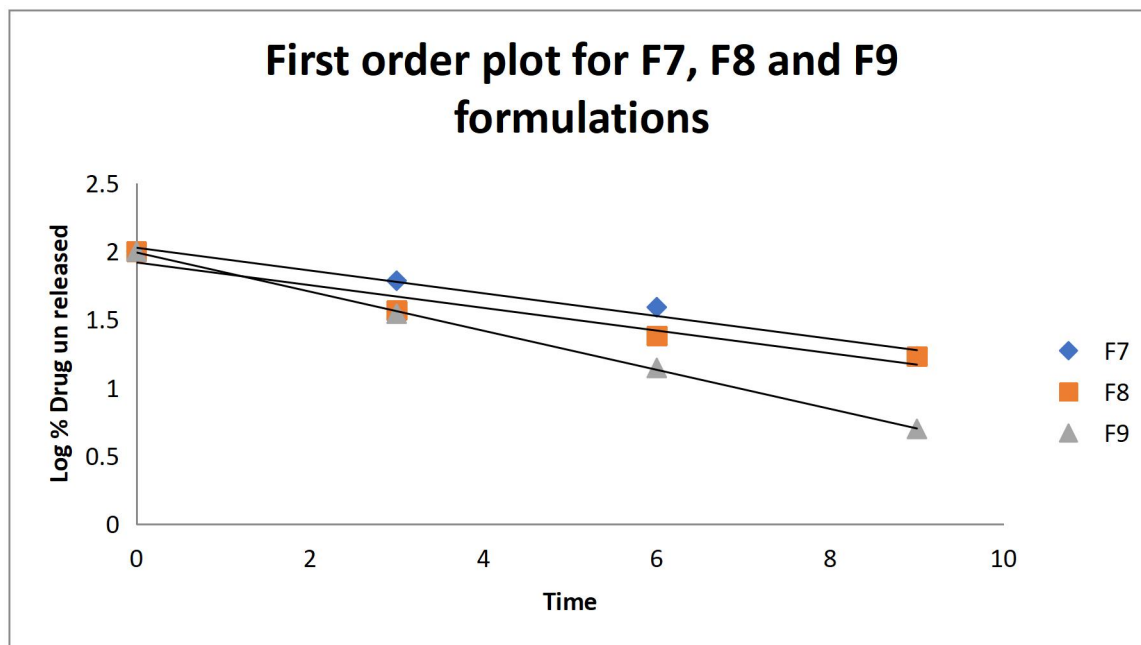


Fig 10 : First order plot for F7, F8 and F9 formulations

Table 6: R2 Values for best formulation F9

Formulation code	Zero order	First order
F9	0.789	0.999

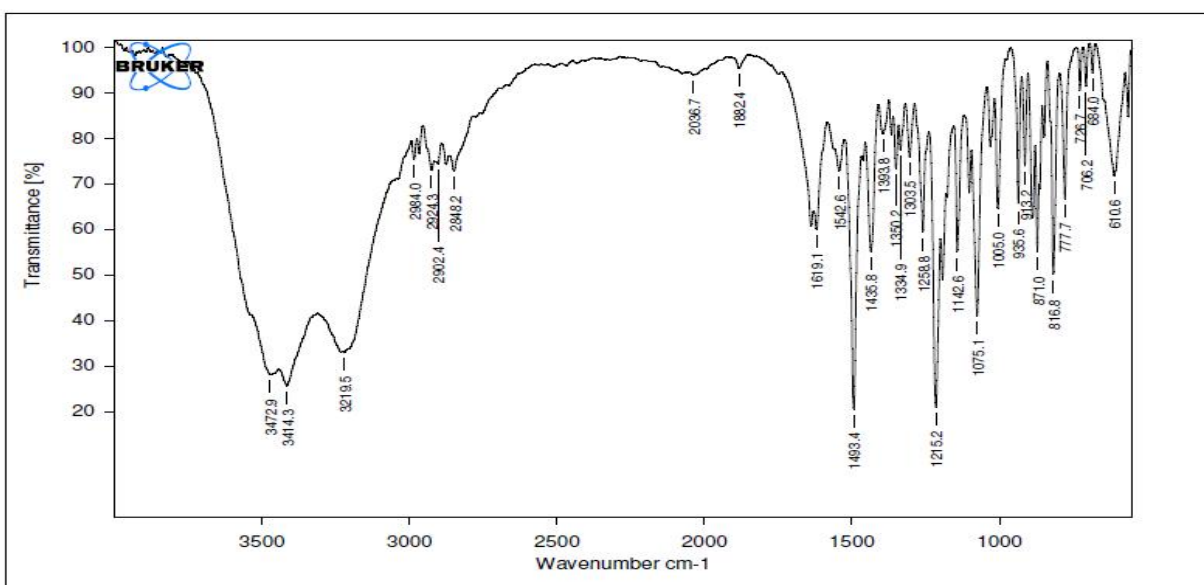


Fig 11: FTIR graph for Risperidone

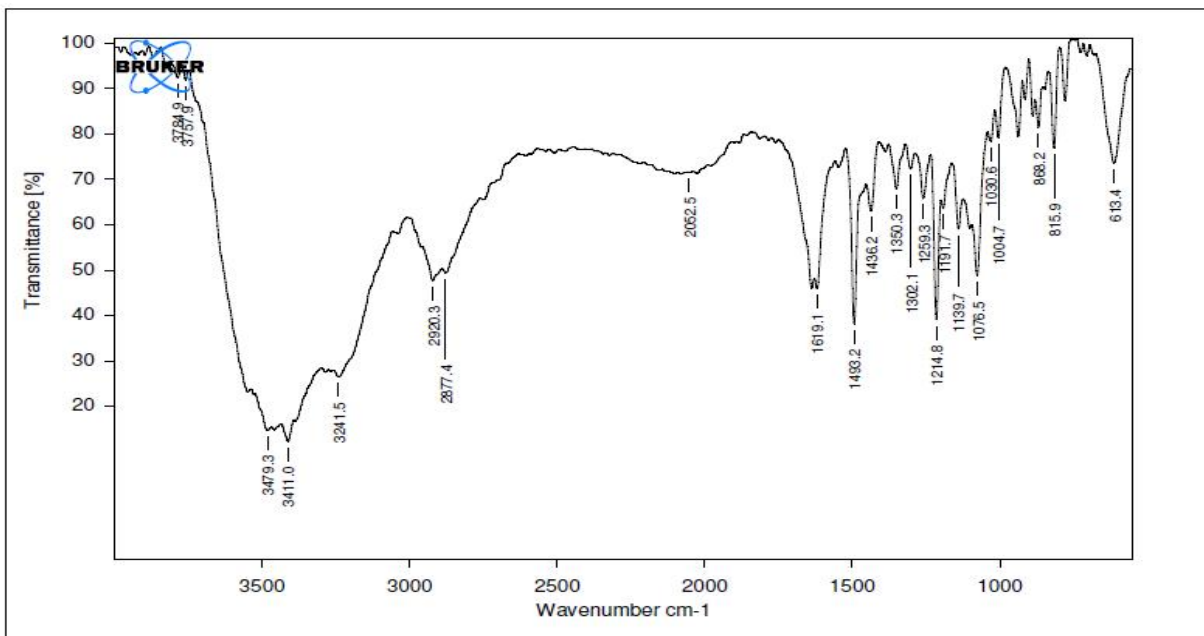


Fig 12: FTIR graph for Risperidone best formulation

“STABILITY STUDIES OF PHYSICAL AND CHEMICAL PARAMETERS”:

‘Selected formulation F4 was strip packed and stored at 40°C ± 2°C / 75% ± 5% RH or a period of 1 month. Samples were analyzed after storage for 1 month and evaluated.’

Table-7: ‘In-vitro release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)’

TIME	Initial	1 Month
0	0	0
3	65	64
6	86	87
9	95	95
12	100	100

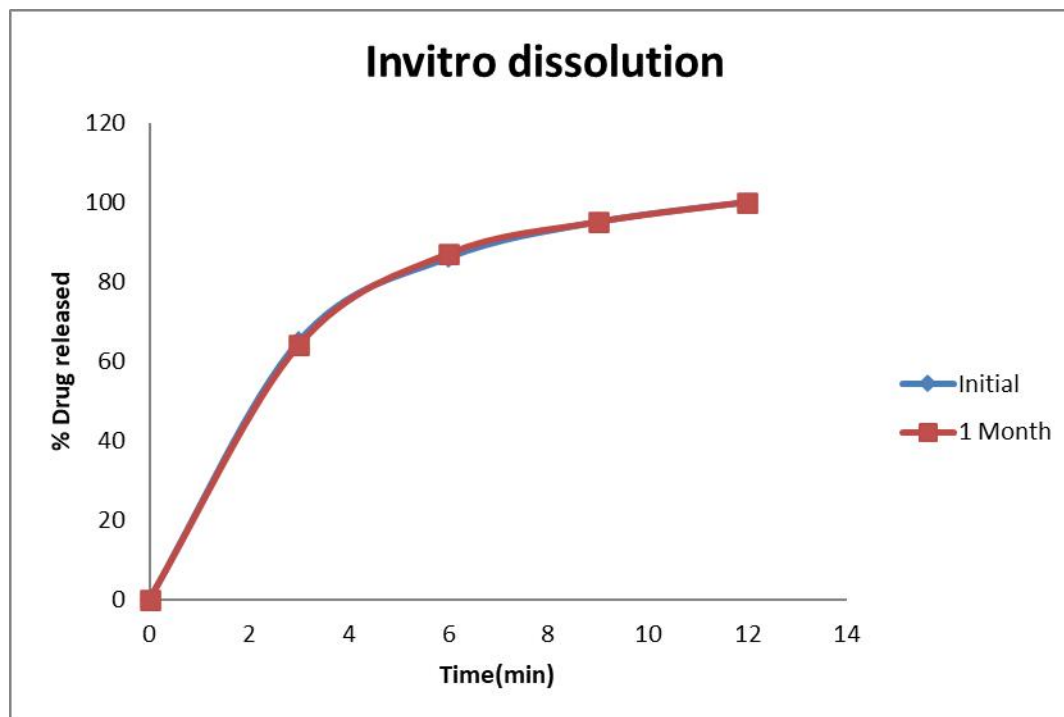


Fig. 13: *In-vitro* release profile of F9 during Stability studies ($40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$)

SUMMARY & CONCLUSION

Risperidone Orally disintegrating films have been successfully manufactured using HPMC E15CPS and a combination of HPMC E15 and HPMC E5. The films exhibited a smooth, elegant surface upon visual and tactile evaluation, with thicknesses ranging from 0.234 mm to 0.271 mm and weights varying within $\pm 10\%$. Their folding endurance was between 38 ± 1 and 57 ± 2 folds, and the surface pH was neutral. Drug content uniformity ranged from 98% to 102%, with disintegration times between 21 and 32 seconds. Batch F-9 showed acceptable mechanical properties and an *in-vitro* disintegration time of less than 27 seconds, making it the optimized formulation with desired properties.

REFERENCES

1. Sharma, D., Kaur, D., Verma, S., Singh, D., Singh, M., Singh, G., & Garg, R. (2015). Fast dissolving oral films technology: A recent trend for an innovative oral drug delivery system. *International Journal of Drug Delivery, 7*, 60-75.

2. Siddiqui, M. D. N., Garg, G., & Sharma, P. K. (2011). A short review on “A novel approach in oral fast dissolving drug delivery system and their patents”. *Advances in Biological Research, 5*, 291-303.
3. DrugBank. (n.d.). Reserpipidone drug profile. Retrieved from <https://go.drugbank.com/drugs/DB00734>
4. Dixit, R., & Puthli, S. (2009). Oral strip technology: Overview and future potential. *Journal of Controlled Release, 139*(2), 94-107.
5. Arya, A., Chandra, A., Sharma, V., & Pathak, K. (2010). Fast dissolving oral films: An innovative drug delivery system and dosage form. *International Journal of ChemTech Research, 2*(2), 576-583.
6. Mashru, C., Sutariya, V., Sankali, M., & Parikh, P. (2005). Development and evaluation of fast-dissolving film of salbutamol sulphate. *Drug Development and Industrial Pharmacy, 31*(1), 25-34.
7. Nishimura, M., Matsuura, K., Tsukioka, T., Yamashita, H., Inagaki, N., Sugiyama, T., & Itoh, Y. (2009). In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. *International Journal of Pharmaceutics, 398*(1-2), 98-102.
8. Shimoda, H., Taniguchi, K., Nishimura, M., Matsuura, K., Tsukioka, T., Yamashita, H., Hirano, K., Yamamoto, M., Kinoshita, Y., & Itoh, Y. (2009). Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. *European Journal of Pharmaceutics and Biopharmaceutics, 73*(3), 361-365.
9. Slowson, M., & Slowson, S. (1985). What to do when patients cannot swallow their medications. *Pharmacy Times, 51*, 90-96.
10. Doheny, K. (1993). You really expect me to swallow those horse pills? *American Druggist, 208*, 34-35.
11. Tora-Tora, G., & Gorahowski, S. (1992). *Principles of Anatomy and Physiology* (7th ed., pp. 770-774). Harper Collins College Publishers.

12. Waugh, A., & Goraw, A. (2001). **Anatomy and Physiology in Health and Illness** (9th ed., pp. 289-293). Churchill Livingstone Edinburgh.
13. OnDrugDelivery.com. (n.d.). Retrieved from <http://www.ondrugdelivery.com>
14. Vondrak, B., & Barnhart, S. (2008). Dissolvable films for flexible product format in drug delivery. **Pharmaceutical Technology Supplement, April 2008**, 1-6.
15. Frey, P. (2006). Film strips and pharmaceuticals. **Pharmaceutical Manufacturing and Packaging Sourcer, 2006**, 92-93.
16. Zhang, H., Zhang, J., & Streisand, J. B. (2002). Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. **Clinical Pharmacokinetics, 41*(9), 661-680.*
17. Barnhart, S. D., & Sloboda, M. S. (2007). The future of dissolvable films. **Drug Delivery Technology, 7*(4), 34-37.*
18. Meathrel, B., & Moritz, C. (2007). Dissolvable films and their potential in IVDs. **IVD Technology, 13*(7), 53-58.*
19. Mishra, R., & Amin, A. (n.d.). Quick API delivery. **Pharmaceutical Technology Europe**, 1-5.
20. Coppens, K. A., Hall, M. J., Mitchell, S. A., & Read, M. D. (2005). Hypromellose, ethyl cellulose and polyethylene oxide used in hot melt extrusion. **Pharmaceutical Technology, September 2005**, 1-6.
21. Patel, R., Naik, S., Patel, J., & Baria, A. (2009). Formulation development and evaluation of mouth melting film of ondansetron. **Archives of Pharmaceutical Science Research, 1*(2), 212-217.*
22. Singh, S., Gangwar, S., Garg, G., Garg, V., & Sharma, P. K. (2010). Formulation and evaluation of rapidly disintegrating film of levocetirizine hydrochloride. **Der Pharmacia Lettre, 2*(2), 434-439.*
23. Shimoda, H., Taniguchi, K., Nishimura, M., Matsuura, K., Tsukioka, T., Yamashita, H., Inagaki, N., Hirano, K., Yamamoto, M., Kinoshita, Y., & Itoh, Y. (2009). Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during

cancer chemotherapy. *European Journal of Pharmaceutics and Biopharmaceutics, 73*(3), 361-365.

24. Cilurzo, F., Cupone, I., Minghetti, P., Selmin, F., & Montanari, L. (2008). Fast dissolving films made of maltodextrins. *European Journal of Pharmaceutics and Biopharmaceutics, 70*(3), 895-900.

25. Dinge, A., & Nagarse, M. (2008). Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. *AAPS PharmSciTech, 9*(2), 349-356.

26. Murata, Y., Isobe, T., Kofuji, K., Nishida, N., & Kamaguchi, R. (2010). Preparation of fast dissolving films for oral dosage from natural polysaccharides. *International Journal of Pharmaceutics, 3*(1), 4291-4299.

27. Mashru, R. C., Sutariya, V. B., Sankalia, M. G., & Parikh, P. P. (2005). Development and evaluation of fast dissolving film of salbutamol sulphate. *Drug Development and Industrial Pharmacy, 31*(1), 25-34.

28. Swamy, P. V., Amitkumar, T., Shirsand, S. B., & Patil, S. (2010). Design and evaluation of buccal patches of granisetron hydrochloride. *Indian Journal of Pharmaceutical Education and Research, 44*(1), 1-8.

29. Panchal, M. S., Patel, H., Bagada, A., & Vadalia, K. R. (2012). Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride using pullulan polymers. *International Journal of Pharmaceutical Sciences and Research, 1*(2), 60-72.

30. Dahiya, S., Asati, S., & Mallurwar, V. (2011). Formulation and evaluation of granisetron hydrochloride orodispersible tablets. *Bulletin of Pharmaceutical Research, 1*(1), 41-46.