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DEVELOPMENT AND CHARACTERISATION OF FEDRATINIB CONTROLLED RELEASE TABLETS

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Abstract: Fedratinib is a selective Janus kinase-2 (JAK2) inhibitor indicated for the treatment of intermediate-2 and high-risk myelofibrosis. The present study aimed to develop and characterize controlled-release matrix tablets of Fedratinib using different concentrations of Ethylcellulose and Eudragit RS100 as release-retarding polymers by the direct compression method. Eight formulations (F1–F8) were prepared by direct compression using Ethylcellulose (F1–F4) and Eudragit RS100 (F5–F8). The prepared tablets showed acceptable weight variation, thickness, hardness, and friability within pharmacopoeial limits. Drug content ranged from 83.69% to 96.80%, with formulation F8 showing the highest drug content (96.80%). In-vitro dissolution studies revealed sustained drug release from all formulations over an 8-hour period. Formulation F8, containing the highest concentration of Eudragit RS100, exhibited the most desirable release profile with 99.55% cumulative drug release at the end of 8 hours. Drug release kinetic analysis indicated that the optimized formulation followed Zero-order kinetics (R^2 = 0.993) and showed a good fit to the Higuchi diffusion model (R^2 = 0.941), suggesting diffusion-controlled drug release. Stability studies conducted at 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH for three months demonstrated no significant changes in drug release, confirming the stability of the optimized formulation.

Keywords: Fedratinib, Controlled-release tablets, Matrix tablets, Eudragit RS100, Ethyl cellulose, Direct compression, In-vitro dissolution, Release kinetics, Stability studies.

INTRODUCTION

Oral drug delivery remains the most widely accepted and convenient route of drug administration owing to its ease of administration, patient compliance, cost-effectiveness, and flexibility in formulation design.1 Controlled release (CR) drug delivery systems have therefore been developed to provide a predetermined rate of drug release over an extended period, maintaining therapeutic plasma concentrations while minimizing peak-to-trough fluctuations.2 Controlled release tablets are among the most successful oral modified-release dosage forms because they are simple to manufacture, chemically stable, and capable of delivering drugs in a predictable manner.3 Fedratinib is a selective Janus kinase 2 (JAK2) inhibitor approved for the treatment of adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis, including post-polycythemia vera and post-essential thrombocythemia myelofibrosis.4 Consequently, the development of a controlled release formulation capable of providing sustained drug delivery has the potential to improve therapeutic performance by maintaining more consistent plasma drug concentrations while minimizing concentration-dependent toxicity.5 Controlled release matrix tablets of fedratinib offer several potential therapeutic advantages. Therefore, the present investigation aims to develop and characterize controlled release tablets of fedratinib using suitable release-retarding polymers to achieve sustained drug delivery. 6

MATERIALS

Fedratinib was procured from Hetero Labs, HYD, Eudragit RS 100 and Ethyl cellulose were obtained from Synpharma

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Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Formulation Development

Table-1: Formulation table of Fedratinib controlled release tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1	Fedratinib	400	400	400	400	400	400	400	400
2	Ethylcellulose	100	200	300	400	-	-	-	-
3	Eudragit RS 100	-	-	-	-	100	200	300	400
4	Microcrystalline Cellulose	395	295	195	95	395	295	195	95
5	Magnesium stearate	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2
7	Total weight	900	900	900	900	900	900	900	900

Preparation method

Fedratinib controlled-release tablets were prepared by the direct compression method. All ingredients were accurately weighed according to the formulation composition shown in Table 3. The required quantities of Fedratinib, Ethyl cellulose or Eudragit RS 100, and Microcrystalline Cellulose (MCC) were individually passed through #60 mesh sieve to remove lumps and obtain uniform particle size. The sieved powders were transferred into a clean, dry mortar or polybag and blended thoroughly for 10–15 minutes to ensure uniform distribution of the drug and polymers. Microcrystalline cellulose was incorporated as a diluent to improve the compressibility and flow properties of the powder blend. After obtaining a homogeneous mixture, talc and magnesium stearate, previously passed through #80 mesh sieve, were added to the powder blend. The mixture was gently blended for an additional 2–3 minutes to avoid over-lubrication while ensuring uniform distribution of the lubricant and glidant. Finally, the lubricated blend was compressed into tablets using a single-station tablet compression machine fitted with 6 mm flat-faced round punches. The compression force was adjusted to produce tablets of approximately 100 mg weight with adequate hardness (about 4–6 kg/cm²) and low friability. The compressed tablets were collected, visually inspected for any defects, and stored in airtight containers at room temperature until further evaluation.7

Evaluation of tablet

Weight Variation

The weight variation test was performed according to the Indian Pharmacopoeia (IP). Twenty tablets were selected randomly from each formulation batch and weighed individually using a calibrated digital analytical balance. The average weight of the tablets was calculated, and the percentage deviation of each individual tablet from the average weight was determined. The tablets were considered to comply with the pharmacopoeial specifications if the weight variation was within the prescribed limits.8

Formula

$$\% \text{ Weight Variation} = \frac{\text{Individual Tablet Weight} - \text{Average Tablet Weight}}{\text{Average Tablet Weight}} \times 100$$

Thickness

The thickness of the tablets was measured using a digital Vernier caliper. Ten tablets were selected randomly from each formulation batch, and the thickness of each tablet was measured individually. The average thickness and standard deviation were calculated and recorded. Uniform tablet thickness is essential for maintaining consistency in tablet size, packaging, and appearance. Tablet thickness indicates the uniformity of compression and helps ensure consistency in tablet dimensions. Uniform thickness also facilitates proper packaging and patient acceptability.9

Tablet Hardness

The hardness of the tablets was determined using a Monsanto hardness tester (or Pfizer hardness tester). Ten tablets were selected randomly, and each tablet was placed between the anvils of the hardness tester. Pressure was applied gradually until the tablet fractured. The force required to break the tablet was recorded in kg/cm², and the average hardness was calculated. Tablet hardness indicates the mechanical strength of the tablets and their ability to withstand handling, packaging, transportation, and storage without breaking. Adequate hardness also influences tablet disintegration and drug release characteristics.10

Typical hardness for controlled-release tablets: 5–8 kg/cm²

Friability

The friability of the tablets was determined using a Roche friabilator. A sample of tablets (usually 20 tablets or tablets weighing approximately 6.5 g) was accurately weighed (W_1) and placed in the friabilator. The apparatus was operated at 25 rpm for 4 minutes (100 revolutions). After completion of the test, the tablets were removed, dedusted, and reweighed (W_2).11 The percentage friability was calculated using the following formula.

% F = {1-(Wo/W)} ×100

Where,

% F = friability in percentage

W o = Initial weight of tablet

W = weight of tablets after revolution

Drug Content

The drug content of the prepared Fedratinib controlled-release tablets was determined by the UV–Visible spectrophotometric method. Ten tablets were weighed individually and finely powdered. A quantity of powder equivalent to 10 mg of Fedratinib was accurately weighed and transferred into a 100 mL volumetric flask. About 70 mL of phosphate buffer (pH 6.8) (or a suitable dissolution medium) was added, and the solution was sonicated for 15–20 minutes to ensure complete extraction of the drug. The volume was then made up to 100 mL with the same solvent and filtered through Whatman No. 1 filter paper. Suitable dilutions were prepared, and the absorbance was measured at the λmax of Fedratinib using a UV–Visible spectrophotometer against a reagent blank. The drug content was calculated using the previously prepared calibration curve. The test was performed in triplicate, and the average percentage drug content was reported.12

Formula

$$\% \text{ Drug Content} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

In-vitro Release Studies13

The in-vitro drug release study of Fedratinib controlled-release tablets was carried out using the USP Dissolution Apparatus Type II (Paddle method). The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. The paddle rotation speed was set at 50 rpm. One tablet from each formulation was placed in the dissolution vessel. At predetermined time intervals (e.g., 1, 2, 4, 6, 8, 10, and 12 hours), 5 mL of the dissolution medium was withdrawn and replaced immediately with an equal volume of fresh dissolution medium maintained at the same temperature to maintain sink conditions. The collected samples were filtered through Whatman No. 1 filter paper, suitably diluted if necessary, and analyzed using a UV–Visible spectrophotometer at the λmax of Fedratinib. The cumulative percentage drug release was calculated using the calibration curve, and dissolution profiles were plotted as cumulative percentage drug release versus time. The dissolution study evaluates the release behavior of the drug from the controlled-release matrix tablets and determines whether the formulation provides the desired sustained-release profile.

Release Kinetics14

The dissolution data obtained from the in-vitro drug release studies were analyzed by fitting them into various mathematical kinetic models to determine the mechanism of drug release. The cumulative percentage drug release data were fitted to Zero-order, First-order, Higuchi, Korsmeyer–Peppas. The correlation coefficient (R^2) for each model was calculated, and the model showing the highest R^2 value was considered to best describe the release kinetics of the optimized formulation. The release exponent (n) obtained from the Korsmeyer–Peppas model was used to identify the drug release mechanism.

Stability studies15

The stability study of the optimized Fedratinib controlled-release tablet formulation was carried out according to the International Council for Harmonisation (ICH) guidelines (ICH Q1A(R2)). The optimized tablets were packed in aluminum foil or HDPE containers and stored under accelerated stability conditions at 40 ± 2°C and 75 ± 5% relative humidity (RH) in a stability chamber for 3 months. Samples were withdrawn at 0, 1, 2, and 3 months and evaluated for physical appearance, weight variation, hardness, friability, drug content, and in-vitro drug release profile. The obtained results were compared with the initial values to assess any significant changes in the physicochemical properties or drug release behavior.

RESULTS AND DISCUSSION

Evaluation parameters

Table-2: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
F1	898	5.86	4.95	0.45	83.69
F2	900	5.91	4.58	0.53	85.79
F3	901	5.80	4.37	0.58	88.75
F4	899	5.99	4.26	0.57	91.25
F5	900	5.82	4.12	0.49	93.38
F6	900	6.20	4.91	0.52	89.82
F7	899	6.08	4.53	0.59	95.57
F8	900	6.28	4.56	0.60	96.80

Discussion

The weight variation of all formulations ranged from 898 to 901 mg, indicating minimal variation among the tablets. All

formulations complied with the pharmacopoeia limits for tablets weighing more than 250 mg (±5%), demonstrating uniform die filling during the compression process and consistent tablet weight. The tablet thickness was found to vary between 5.80 and 6.28 mm. The slight increase in thickness observed in formulations containing higher concentrations of polymer, particularly F6–F8, may be attributed to the greater proportion of Eudragit RS100, which increases the tablet volume. Nevertheless, the variation in thickness among the formulations was minimal, indicating uniform compression and consistent tablet dimensions. The hardness of the tablets ranged from 4.12 to 4.95 kg/cm², which is considered acceptable for controlled-release matrix tablets. Formulation F1 exhibited the highest hardness (4.95 kg/cm²), whereas F5 showed the lowest hardness (4.12 kg/cm²). Overall, all formulations possessed sufficient mechanical strength to withstand handling, packaging, and transportation without significant breakage while still allowing controlled drug release. The friability values ranged from 0.45% to 0.60%, which are well below the pharmacopoeial limit of 1.0%. Formulation F1 showed the lowest friability (0.45%), indicating excellent resistance to abrasion, while F8 exhibited the highest friability (0.60%). However, all formulations demonstrated adequate mechanical integrity and durability for routine handling. The drug content of the formulations ranged from 83.69% to 96.80%. An increasing trend in drug content was observed from F1 to F8, with F8 showing the highest drug content (96.80%) and F1 the lowest (83.69%). Formulations F7 (95.57%) and F8 (96.80%) complied with the generally accepted pharmacopoeial specification of 95–105% of the labeled claim, indicating uniform drug distribution. However, formulations F1–F6 exhibited drug contents below the acceptable range, suggesting incomplete blending, segregation of the drug during mixing, or inadequate mixing time. These findings indicate that optimization of the blending process or formulation composition may be required to improve drug content uniformity in these formulations.

In-vitro Dissolution Study

Table-3: In vitro release data of tablet F1 to F8

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	18.89	19.20	17.20	16.89	19.82	17.69	16.39	20.25
2	28.47	27.46	27.52	28.58	27.46	29.25	25.57	31.25
3	35.61	32.24	34.39	31.17	36.55	37.84	35.48	41.25
4	48.50	45.63	46.35	47.83	49.86	50.25	49.86	51.32
5	58.99	57.49	57.16	58.55	59.43	61.23	63.35	67.85
6	74.51	75.21	75.12	72.34	76.23	77.85	78.88	79.86
7	82.35	83.26	80.20	85.46	84.58	85.98	87.86	89.28
8	95.58	96.38	93.98	96.81	97.42	95.55	97.25	99.55

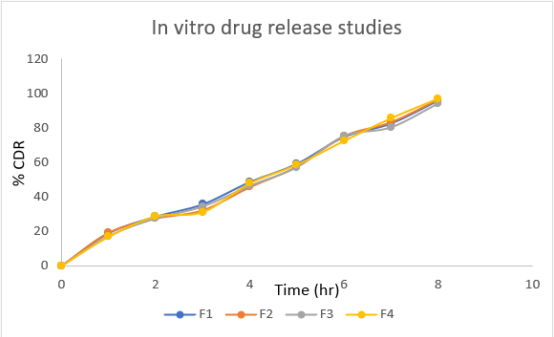


Fig-1: In vitro drug release studies of F1-F4 formulations

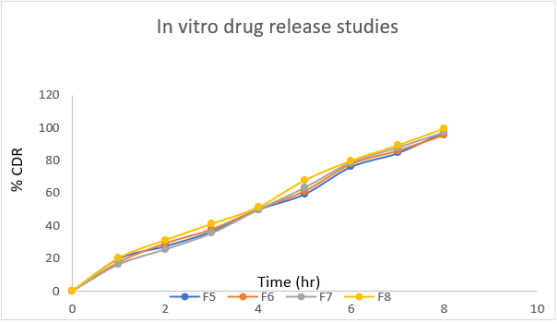


Fig-2: In vitro drug release studies of F4-F8 formulations

Discussion

Overall, the dissolution results indicated that both polymers successfully retarded drug release; however, Eudragit RS100 produced a more controlled and reproducible release profile than Ethyl cellulose. Among all formulations, F8 showed the highest cumulative drug release (99.55%) with a consistent release pattern and was therefore selected as the optimized formulation for further kinetic analysis

Kinetic modelling of drug release

All the 8 formulations of prepared matrix tablets of Fedratinib were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)

2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Pappas Exponential Equation)

Zero order kinetics

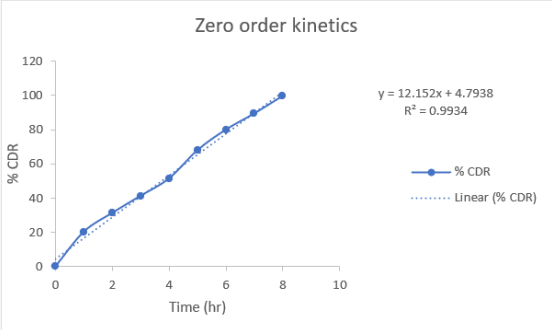


Fig-3: Zero order kinetics of optimized formulation

First order kinetics

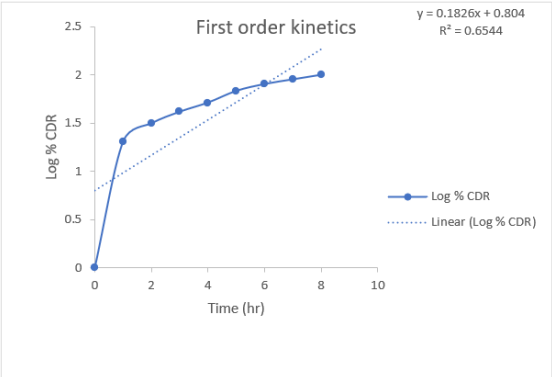


Fig-4: First order kinetics of optimized formulation

Higuchi model

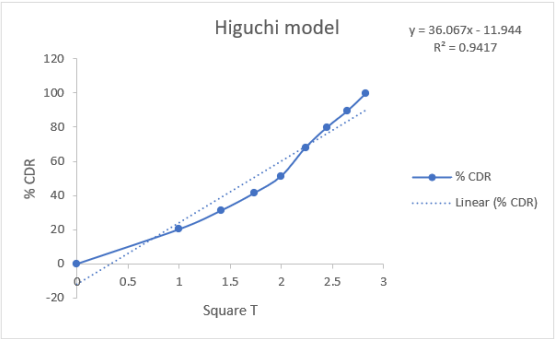


Fig-5: Higuchi model of optimized formulation

korsmeyer peppas

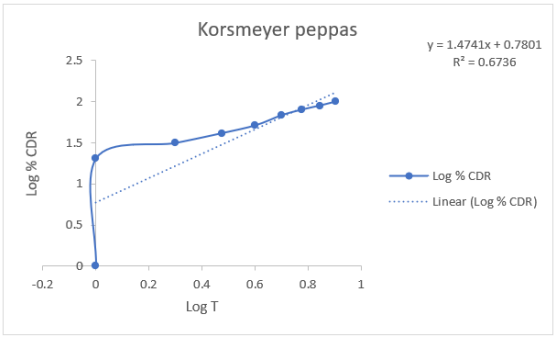


Fig-6: korsmeyer peppas of optimized formulation

Discussion

Based on the kinetic analysis, it can be concluded that the optimized Fedratinib controlled-release tablet (F8) predominantly followed Zero-order release kinetics, with diffusion through the polymer matrix contributing substantially to the sustained drug release, as evidenced by the good fit to the Higuchi model.

Stability studies

Table-4: Results of stability studies of optimized formulation F8

Formulation Code	Parameters	Initial	1st Month	2nd	3rd	Limits as per Specifications
F-8	250C/60%RH	99.55	98.36	97.48	96.83	Not less than 85%
F-8	300C/75% RH	99.55	98.52	97.36	96.28	Not less than 85%
F-8	400C/75% RH	99.55	98.21	97.25	96.13	Not less than 85%

Discussion

The overall stability results demonstrate that no significant changes occurred in the dissolution profile of the optimized formulation during the storage period. The tablets retained their controlled-release characteristics even under accelerated conditions, indicating good compatibility between Fedratinib, Eudragit RS100, and the other excipients. The polymer matrix remained intact, preventing any substantial alteration in drug release behavior. These findings confirm that the optimized formulation F8 possesses excellent stability under long-term, intermediate, and accelerated storage conditions. The formulation complied with the specified acceptance criteria throughout the three-month study and maintained its controlled-release performance. Therefore, F8 can be

considered a physically and chemically stable controlled-release tablet formulation with the potential for an adequate shelf life under recommended storage conditions.

CONCLUSION

The present investigation successfully developed Fedratinib controlled-release matrix tablets using the direct compression technique with Ethyl cellulose and Eudragit RS100 as release-retarding polymers. The prepared formulations exhibited satisfactory pre-compression and post-compression characteristics, indicating good powder flow, compressibility, tablet integrity, and manufacturing suitability. Among all the formulations, F8, containing 400 mg of Eudragit RS100, was identified as the optimized formulation because it demonstrated excellent physical properties, satisfactory drug content, and the highest cumulative drug release (99.55%) over 8 hours. Drug release from the optimized formulation followed Zero-order kinetics with diffusion-controlled release characteristics, making it suitable for sustained drug delivery. The optimized formulation also remained stable under 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH storage conditions for three months, with no significant changes in the dissolution profile. These findings indicate that the formulation possesses good stability and has the potential to maintain its quality during storage. Overall, the study demonstrates that Eudragit RS100 is an effective release-retarding polymer for the development of Fedratinib controlled-release tablets. The optimized formulation has the potential to provide prolonged drug release, reduce dosing frequency, improve patient compliance, and maintain consistent therapeutic drug levels.

REFERENCES

[1]. Harrison CN, Schaap N, Vannucchi AM, Kiladjian JJ, Tiu RV, Zachee P, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): A single-arm, open-label, non-randomised, phase 2, multicenter study. The Lancet Hematology. 2017;4(7):e317–e324.

[2]. Pardanani A. Fedratinib, a selective JAK2 inhibitor, for the treatment of myelofibrosis. Blood Cancer Journal. 2020;10:94.

[3]. FDA. INREBIC® (Fedratinib) Capsules: Prescribing Information. U.S. Food and Drug Administration; 2019.

[4]. Goodman LS, Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 14th ed. New York: McGraw-Hill Education; 2023.

[5]. Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 6th ed. Elsevier; 2022.

[6]. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 4th ed. CBS Publishers & Distributors; 2019.

[7]. Colombo P, Bettini R, Santi P, De Ascentiis A, Peppas NA. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. Journal of Controlled Release. 1996;39(2–3):231–237.

[8]. Siepmann J, Peppas NA. Hydrophilic matrices for controlled drug delivery: An improved mathematical model to predict the resulting drug release kinetics. Pharmaceutical Research. 2000;17(10):1290–1298.

[9]. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica. 2010;67(3):217–223.

[10]. Kamalakkannan V, Puratchikody A, Masilamani K, Saraswathy T. Analytical method development and validation for Candesartan Cilexetil as bulk drug and in pharmaceutical dosage forms by HPLC. Der Pharmacia Lettre. 2011;3:286–296. [Google Scholar]

[11]. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci. 1961;50:874–875.

[12]. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of potassium chloride release from compressed, hydrophilic, polymeric matrices: Effect of entrapped air. J Pharm Sci. 1983;72:1189–1191.

[13]. Mathew ST, Devi SG, Prasanth VV, Vinod B. Formulation and in vitro-in vivo evaluation of ketoprofen-loaded albumin microspheres for intramuscular administration. J Microencapsulate. 2009;26:456–469.

[14]. Shinde, S. ., & Chaurasia, G. . (2025). Formulation Development and Characterization of Ritonavir Loaded

Controlled Release Matrix Tablet. Current Trends in Biotechnology and Pharmacy, 19(2), 2294–2302.

[15]. Kumar KK, Reddy NM, Kishore NR. Formulation and Evaluation of Bilayer matrix tablet of Pioglitazone HCl and Metformin HCl USP 15MG & 500MG. Asian J Pharm Clinical Research. 2013; 6(3):155–161

[16]. Patel JA, Panigrahi B, Patel CN. Development and validation of

[17]. a UV spectrophotometric method for estimation of Citicoline

[18]. sodium in Bulk and Dosage Form. Journal of Pharmacy

[19]. Research; 2010; 3 (12):2876-2878.