American Journal of Drug Delivery and Therapeutics
a Pubicon Open Journal

RESEARCH OPEN ACCESS

Formulation Development and Physico-Chemical Study of Epalrestat Tablet with Improved Bioavailability in Terms of Disintegration and Dissolution

Swapon Kumar Biswas, Sujit Biswas*, Jamilur Rahman Bhuiyan, Md. Abdullah-Al-Mamun, and Sukalyan Kumar Kundu

Department of Pharmacy, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh

Email Id:
sujitpharm@gmail.com

Abstract

Experiments were conducted on Epalrestat 50 mg tablet which is antidiabetic drug that is used for the treatment peripheral diabetic neuropathy as well as diabetic neuropathy. Six study which were coded as F-1, F-2, F-3, F-4, F-5&F-6 were conducted to optimize the formulation to find out the better formulation that exhibits good systemic bioavailability. The active material of this formulation was collected from Cangzou senary Chemical S. & T. Co., Ltd., China. The local agent of this active is ASN Corporation. All of these formulations conducted in accordance with strong cGMP guidelines. The first three formulations were done through direct compression method but last two, formulated through wet granulation method. Then coating operation was performed for the formulation-05 to ensure good aesthetic value and taste and also to protect the drug from moisture. Then certain quality control tests (e.g. Thickness, Individual weight, Hardness, Friability Disintegration and dissolution) were carried out for the formulation-05, the final formulation. The assay content of Epalrestat were calculated by UV-instrumental method which was developed for getting convenient and cost effective result. Test was carried out at 400 nm wavelength .The dissolution test of six tablets of the final formulation were also performed and the result of dissolution test performed through dissolution test apparatus-II (paddle method) with phosphate Buffer (PH=7.2) with 75 Rotation per minute and it exhibited better result that ensure good bioavailability by means of enhanced dissolution property.

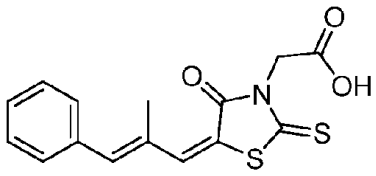
Keywords- Antidiabetic, Bioavailability, Wet granulation, Diabetic neuropathy and Wavelength.

Introduction

Epalrestat is Oral anti diabetic agent, Aldose reductase inhibitor which is a carboxylic acid derivative which inhibits aldose reductase, an enzyme of the sorbitol (polyol) pathway. Under hyperglycemic conditions epalrestat reduces intracellular sorbitol accumulation, which has been implicated in the pathogenesis of late-onset complications of diabetes mellitus[1-4,13]. Epalrestat 150 mg/day for 12 weeks improved motor and sensory nerve conduction velocity, and vibration threshold compared with baseline and placebo in patients with diabetic neuropathy[6]. Subjective symptoms including pain, numbness, hyperaesthesia, coldness in the extremities, muscular weakness, dizziness, and orthostatic fainting were also improved. Similar benefits were seen in a comparison with historical controls. Epalrestat 300 mg/day for 1 or 3 years was also significantly superior to placebo or no treatment in improving electroretinogram parameters and photo stress recovery time in patients with diabetic retinopathy[3-4]. Improvements were also documented by funduscopy and fluorescein angiography. Epalrestat appeared most effective in patients with less severe diabetes mellitus and more recent.

Long-term treatment with epalrestat is well tolerated and can effectively delay the progression of diabetic neuropathy and ameliorate the associated symptoms of the disease, particularly in subjects with good glycemic control and limited microangiopathy[6]. Natural sources reported to inhibit aldose reductase include spinach, cumin seeds, fennel seeds, basil leaves, lemon, black pepper, orange, curry leaves, and cinnamon. Chemical name of Epalrestat is C15-H13-N-O3-S2 (5-[(Z, E)-β-Methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid) and

its molecular weight is 319.



Epalrestat

Diabetic neuropathy is one of the most common long-term complications in patients with diabetes mellitus, with a prevalence of 60-70% in the United States. Treatment options include antidepressants, anticonvulsants, tramadol, and capsaicin. These agents are modestly effective for symptomatic relief, but they do not affect the underlying pathology nor do they slow progression of the disease[6]. Epalrestat is an aldose reductase inhibitor that is approved in Japan for the improvement of subjective neuropathy symptoms, abnormality of vibration sense, and abnormal changes in heart beat associated with diabetic peripheral neuropath. Unlike the current treatment options for diabetic neuropathy, Epalrestat may affect or delay

progression of the underlying disease process. Data from experimental studies indicate that epalrestat reduces sorbitol accumulation in the sciatic nerve, erythrocytes, and ocular tissues in animals, and in erythrocytes in humans. Data from six clinical trials were evaluated, and it was determined that epalrestat 50 mg 3 times/day may improve motor and sensory nerve conduction velocity and subjective neuropathy symptoms as compared with baseline and placebo. Epalrestat is well tolerated, and the most frequently reported adverse effects include elevations in liver enzyme levels and gastrointestinal-related events such as nausea and vomiting. Epalrestat may serve as a new therapeutic option to prevent or slow down the progression of diabetic neuropathy[3]. For this reason, bioavailability plays a pivotal role for the efficacy of this product, which can be evaluated by *In-vitro* dissolution study. This circumstance demands a well formulation which can ensure good tablet properties with better disintegration and dissolution by means of using a effective super disintegrant, cross carmelose sodium and well suited binder, Hydroxy propyl cellulose which may provide highly bio available tablet in terms of disintegration and dissolution[7-12]. Although long-term, comparative studies in diverse patient populations are needed for clinical application.

Materials and Method

Materials, reagent, equipment and instruments

Following materials, reagent, equipment and instruments are used to establish the formula. List of materials, equipment and instruments with its purpose of use is given below the table No. 2.1.

Table 2.1. List of materials and its purpose of use

Name of materials	Purpose of use
Epalrestat	Active Pharmaceuticals Ingredients
Cross carmellose sodium	Disintegrant
Magnesium sterate	Lubricant
D-Mannitol	Diluent
Hydroxy propyl cellulose	Binder
Opadry (Orange)	Coating agent
Reagents	**Purpose of use**
Potassium dihydroghen phosphate	Buffering agent
Sodium hydroxide	pH adjusting agent
Phosphoric acid	pH adjusting agent
Methanol	Solvent/Diluent
Purified water	Solvent/Diluent
Instrument	**Name & Origin**
Granulation Machine	Euroven , UK.
Vibratory sieving Machine	Russel Sieve, USA.

Blender Machine	Matcon, USA.
Compression Machine	Majesty, UK.
Coating Machine	Pam Glat, India.
Volumetric Flask, Sonicator, stop watch, Heater, pipette and Mortar and Pestle	N/A
Weighing Balance	Mettler Toledo
UV-Spectrophotometer	SHIMADZU, Japan
Disintegration test apparatus	Erweka, Germany
Dissolution test Apparatus	Mettler Toledo
Roche friabilator	Thermonik, Bombay-400 025, India
Tablet hardness tester	Erweka, Germany

Preparation of core tablets

Core tablets were prepared by direct compression and wet granulation method. All the formulas are denoted by the capital letter F with numeric number 1, 2, 3 etc. For each formulation, the calculated amount of ingredients was weighed, mixed with excipients and sieved properly. In formula 1, accurate quantity of HPC (Klucel EF) and D-Mannitol is dispensed then Sieved through 30mesh screen one after another and Mixed for 5min at 15rpm. Accurate quantity of Crosscarmellose Sodium and Epalrestat (average potency is about 100%) is dispensed and sieved through 30mesh screen one after another and mixed for 5min at 15rpm in another poly bag. Second step materials is poured into the step one in a poly bag and mixed them for 5min at 15rpm. Then dispensed quantity of Magnesium Stearate is added into the poly bag by sieveing through 30mesh and mixed for another 3min at 15rpm and finally compressed into Tablet through 7.5 mm round shallow concave Punch and taking tablet weight 180mg. Formulations of core tablets are shown in the following table No. 2.2.

Table 2.2. List of excipients and amount required to develop the desired formula of Epalrestat tablet

Name of materials	Formula no.	Unit formula		Quantity/Batch	
		Mg/tablet	%	Theoretical qty. (gm)	Dispensed qty. (gm)
Epalrestat	F-1	50	27.78	138.9	139.73
	F-2	50	27.78	138.9	139.73
	F-3	50	27.78	138.9	139.73
	F-4	50	35.71	178.57	178.57
	F-5	50	35.71	178.57	178.57
	F-6	50	35.71	178.57	178.57
D-mannitol	F-1	117	63.33	316.65	316.65
	F-2	114	63.33	316.65	316.65
	F-3	114	63.33	316.65	316.65

	F-4	81	57.86	289.30	289.30
	F-5	77.8	55.57	277.86	277.86
	F-6	77.8	55.57	277.86	277.86
HPC (klucel LF)	F-1	6	3.34	16.7	16.7
	F-2	9	5	25.00	25.00
	F-3	8	4.45	22.25	22.25
	F-4	3	2.14	10.71	10.71
	F-5	5	3.57	17.86	17.86
	F-6	5	3.57	17.86	17.86
Croscarmellose Sodium	F-1	6.5	3.61	18.05	18.05
	F-2	6.5	3.61	18.05	18.05
	F-3	6.5	3.61	18.05	18.05
	F-4	3	2.14	10.71	10.71
	F-5	6	4.28	21.40	21.40
	F-6	6.2	4.43	22.14	22.14
Magnesium stearate	F-1	0.5	0.28	1.4	1.4
	F-2	0.5	0.28	1.4	1.4
	F-3	1.5	0.83	4.15	4.15
	F-4	3	2.14	10.71	10.71
	F-5	1.2	0.86	4.29	4.29
	F-6	1.0	0.71	3.57	3.57
Target individual weight / Tablet	F-1	180	N/A	N/A	N/A
	F-2	180	N/A	N/A	N/A
	F-3	180	N/A	N/A	N/A
	F-4	140	N/A	N/A	N/A
	F-5	140	N/A	N/A	N/A
	F-6	140	N/A	N/A	N/A
Coating materials for formula F-5 & F-6	Opadry - (Orange) II-85G53876	5	14	25	25
	Purified Water	43	86	154	154
Total study batch size of each formula (F-1 toF-6) with product label claim	500gm or 3571 Tablets and Each Tablet contain 50mg Epalrestat				

For F-1, Capping and lamination was found for almost all the tablets. For the purpose of optimizing formulation the concentrations of all excipients were changed and try to find the better formulation and overcome the problem which results in formula F-2. In F-2, tablets are compressed into 7.5 mm round convex Punch. In case of F-2, capping and lamination was also observed and binder was changed significantly. So to optimize the

formulation another study was undertaken. The concentration of binder increase significantly which triggered the formula F-3. In F-3, Changed have been done by changing quantity mannitol because mannitol has more binding property. Capping and lamination was reduced slightly than the problem observed in formulation F-2. Already three formulations have done and nothing optimistic sign was observed regarding tablet properties. Next formulation was performed through wet granulation because formulation through direct compression showed capping and poor hardness with friability problem as well as high filled weight of tablet (180 mg). Dry granulation was not performed because it would require slugging and milling operation which might add extra cost and more process steps. In F-04, formula, accurate quantity of HPC (Klucel LF) 10.71gm was weighrd and dissolved in 143gm Purified water. Accurate quantity of Epalrestat, D-Mannitol & Crosscarmellose Sodium was weighed and sieved through 20 mesh screen one after another in a poly bag and blend for 5 min at 15 rpm. Step 1 materials was added to the step 2 and mix manually until desire granules form. Granules are dried until LOD NMT (not more than) 1.5-3.0% at 105°C. Magnesium Stearate 2.11gm was weighed and sieved through 30mesh screen and mixed for 3min at 15rpm and then finally compressed into tablet through 7.5 mm round convex Punch and specification was followed as per below table 2.3. During compression ledge breaking problem is found about 5% of tablets and lamination problem found approximately 1% of tablets. May be due to lower LOD (1.5%) and excess binding property of HPC (Klucel LF).The breakdown of trablet during compression or coating is one of the most importatant formulation related problem .So, for overcoming the problem we followed another formulation F-05 again by appling less exposure time of drying and readjustment of quantity of lubricant and binder with diluent to rise the LOD of the granules and other properties which was given good tablet properties except slight edge breaking during coating among the others formulations. Here it is mention that although the formulation F-05 showed good tablet properties and m*et al*l the specification as per table no.2.3, it showed relatively higher disintegration time which might affect the dissolution property, the ultimate goal of study to assure improved bioavailability. Then formulation process was fine tuned finally to achieve the goal properly. This is denoted by formulation F-06. In process, after adding magnesium stearate, final blending was done 2 min at 15 rpm instead of 3 min and slightly reduction of lubricant with the increase of Croscarmellose Sodium. Although the hardness was increased but keeping within range and that's why extra addition of croscarmellose Sodium is added to improve disintegration time.

LOD% of granules and compression parameters were maintained as per table (Table 2.3).

Table 2.3. Tablet specification of final blend with reference

Parameter	Specification	Reference
LOD of granules	(1.5 to 3) %	In house
Individual weight	140 mg ± 5%	In house
Average weight (10 Tablets)	1.4 ± 3%	In house
Pre-compression pressure	13.20 KN	In house
Main compression pressure	22.0 KN	In house
Machine speed	1806 Tablets / minutes	In house
Feeder speed	22 RPM	In house
Hardness	4 – 10 KP	In house
Thickness	(2.85 - 2.99) mm	In house
Disintegration	Not more than 15 minutes at 37°C.	USP
Dissolution Rate	Not less than 70 % of the label claim of Epalrestat dissolved in 45 minutes at 37ºC	USP
Friability	<1.0% w/w	USP
Appearance	A pinkish orange round shallow biconvex tablet. Both sides are plain.	In house
Assay	45–55 mg / Tablet	USP

Coating of core tablets

Take 154.00 gm of Purified Water is weighed and taken into a suitable container and 5 gm of Opadry –OY-P-33107 (Orange) is added. Solution is prepared by stirring at the fastest possible rate, without incurring powder flotation, to the vortex. It may be necessary to increase the stirrer speed in order to maintain a vortex as addition of the pre-mixing powder proceeds, due to a rise in suspension viscosity. After that stirrer speed is reduce the stirrer speed until the vortex is just eliminated and continuous stirring for at least 30 minutes, after which the dispersion will be complete. Prior to load the core tablets, the coating bed temperature is pre warmed to 40- 45^0 C for about 15 minutes. Tablets are then loaded in the pan. After spraying, coated tablets are dried at 50^0 C for about 25 minutes. Coating parameters are set according to below table no. 2.4.

Table 2.4. The set parameters range of greatide coating machine for coating operation

Parameter	Unit	Set range
Outlet air temperature	^{0} C	50-55
Pan Speed	rpm	4-12
Spray gun atomizing air pressure	psi	40-50
Fluid pressure	psi	15-20
Negative pressure	cm	1
Spray rate	ml / min	25
Gun distance from tablet bed	cm	30.48

Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability, content uniformity. The hardness & thickness were measured by erweka Hardness tester. Friability/ abrasion test was performed by using Roche friabilator.

Disintegration test

Six tablets were placed into 6 tubes of disintegration testing apparatus. Disc was added to each tube and suspended the tubes in a 1000 ml beaker having 800ml of purified water maintaining temperature of water from 36.5 ˚c to 37.5 ˚c. 800 ml of water is require to maintain that the wire mesh at its highest point is at least 25 mm below the surface of water and the lowest point is at 25mm above the bottom of the beaker.

Dissolution

In-vitro drug dissolution study of the prepared coated tablets were conducted for a period 45 minutes using an USP dissolution apparatus-11 (paddle system) which was set at 75 rpm and a temperature of 37˚c ± 0.5 ˚c. 900 ml Phosphate buffer (KH_2PO_4) was used as medium and P^H was adjusted to 7.2. The amount of drug released was calculated through UV-VIS spectrophotometer, SHIMADZU, JAPAN by plotting standard concentration against absorbance constructed in the dissolution media. According to USP absorbance of both standard and sample was measured at 400nm (λ_{max}).

Drug content assay

Drug content of prepared tablets was calculated by following USP method.

Performance of UV-Visible Instrumental method

Epalrestat working standard equivalent to 50 mg was taken into a 100ml volumetric flask and then diluted with methanol 60 to 70ml and shook

for 1min. Sonicated for 1min then shook again. Repeated the process until clear transparent solution free from visible orange-red particle of Epalrestat is observed. Volume was adjusted with the methanol and shake. 2ml solution of first dilution was taken into 200ml volumetric flask and diluted with purified water and mixed well. Absorbance was taken at 400nm after making blank (purified water) absorbance zero. For preparation of sample, 20 Tablets were weighed and crushed to make powder and weighed again. The powder was taken into 100 ml volumetric flask and diluted with 60-70 ml methanol and shook well for 1 minute, then sonicated for 1 minute and repeated this step until clear transparent solution free from visible orange-red particle of Epalrestat is obtained. Finally, volume was adjusted. 2 ml of sample was taken into 200ml volumetric flask and diluted with purified water and shook well. Absorbance was taken at 400nm after making blank (purified water) absorbance zero. As a precautionary, care was taken during sonication because Prolong sonication may have degradation tendency and Standard and Sample may degrade on bench top, so prepare within optimize time to minimize all intervals between steps. Assay was measured finally, by putting values in the following formula.

Calculation formula:

Absorbance of Sample X Standard Wt X 2 X 100 X 200 X Tablet Average Wt X Potency / Absorbance of Standard X 100 X 200 X Sample Weight X 2 X 100.

Result and Discussion

All the resulting data of tablet parameter including individual weight, thickness, hardness, friability and disintegration time are presented for core tablet and dissolution and assay are considered for coated tablets because the problematic formulations were rejected while any non compliance of quality at core tablet stages. Coated tablet is the ultimate status for this Epalrestat tablet. The LOD% of granules of formulations F-04, F-05 and F-06 are 1.5%, 1.8% and 2.1% respectively. The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of a tablet can be manually determined with the help of micrometer calipers. The variation in thickness leads to weight based counting and primary packing problems.

Capping and lamination found almost all the tablet from the formula F-01 to F-04. For this reason quality evaluation was not performed for the formulations F-01 to F-04. In case of tablets from F-04, capping was reduced but it was not satisfactory. The reason of capping reduction may be due to

granules processed by wet granulation. Disintegration time is higher than 15minutes. Next trial was done by taking extra amount of binder and disintegrating agent. Due to the existence of disintegrating problem and little amount of capping, thickness test of this formulation was not performed. The partial separation of top and bottom crown of the tablet is significant. Separation of tablet into two or more distinct layers also occurred. Some steps were taken to remove capping and lamination that also hampered the thickness of the tablet. These steps were respectively slowing tabletting rate, by reducing the pressure adjustments, by reducing the speed of the machine, by replacing the worn out dies and punches, by changing the wear and tear of the punches and dies. For the purpose of optimizing formulation the concentrations of all excipients were changed and tried to find the better formulation to overcome the problem. The Formulation F-05 was considered free from all problems during compression although very little lamination problem approximately 0.5%. The thickness of the Formulation F-05 was taken into consideration. Thickness of 10 tablets from F-05 is given below table 2.5.

Table 2.5. Thickness of 10 tablets from F-05

Tablet serial No.	Individual thickness (mm)	Maximum thickness (mm)	Minimum thickness (mm)	Average thickness (mm)	Target thickness (mm)
01	2.95	3.00	2.85	2.93	(2.85-3.0)
02	2.85				
03	2.97				
04	2.88				
05	3.00				
06	2.89				
07	2.92				
08	2.97				
09	2.95				
10	2.94				

Graphical Representation of the thickness of 10 tablet of formulation F-05 given below Fig no. 4.1.

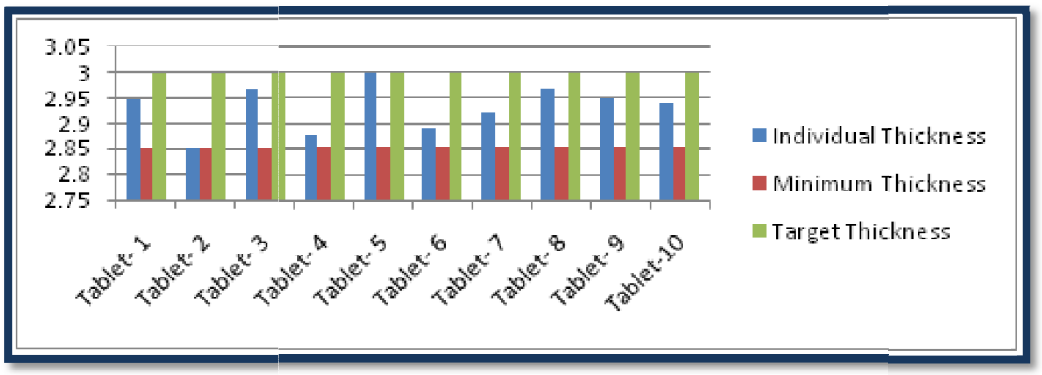


Figure 4.1. Thickness of Formulation F-05

The highest thickness value was showed by the tablet no. 04 and it was 3.00 mm which was at the terminal point of the target limit. So we would precede the final formulation F-06 by considering reduced thickness because this higher thickness can be problematic during the blistering Operation although average thickness value within the target limit.

F-06 formulation was considered as the final formulation. Because it is free from all the tabletting problem and also minimal thickness, no capping, sticking and rough surface during compression and coating was observed.

Table 2.6. Thickness of 10 tablets from F-06

Tablet serial No.	Individual thickness (mm)	Maximum thickness (mm)	Minimum thickness (mm)	Average thickness (mm)	Target thickness (mm)
01	2.85	2.99	2.85	2.94	(2.85-2.99)
02	2.85				
03	2.91				
04	2.99				
05	2.97				
06	2.96				
07	2.92				
08	2.97				
09	2.96				
10	2.94				

The highest thickness value of the tablet no. 05 and it was 2.99 which were within the target limit. Average thickness value was within the target limit. So the problem occurred due to the high thickness that might be problematic during blistering operation that was overcome. The hardness of tablet depends on the weight of the material used, space between the upper and lower punch at the time of compression and pressure applied during compression. The hardness also depends on the nature and quantity of excipient used during formulation.

If the tablet is too hard, it may not disintegrate in the required period of time and if the tablet is too soft it may not withstand the handling during packing and transporting. Therefore it is very necessary to check hardness of tablets when they are being compressed and pressure should be adjusted accordingly on the tablet machine**.** The hardness test of the first four formulations coded as F-01, F-02, F-03, F-04 were not performed due to the basic problem during compression like capping and lamination, thickness and disintegrating problem. The Formulation F-05 was considered due to its good tablet property except little lamination problem during coating. This is because of less LOD% of granules which was overcome in formulation F-06. Hardness was also relatively increased to reduce thickness than formulation F-05 due to application of more compression force.

Table 2.7. Hardness of 10 tablets from F-05

Tablet serial No.	Individual hardness (KP)	Maximum hardness (KP)	Minimum hardness(KP)	Average hardness(KP)	Target hardness(KP)
01	8.15	8.15	5.20	6.89	(4-10)
02	6.10				
03	5.20				
04	7.59				
05	6.36				
06	7.10				
07	6.32				
08	8.14				
09	7.32				
10	6.56				

The highest hardness of the final formulation was found for the tablet no.01 and it was 8.15 KP and the average hardness value within the target limit. The target limit of hardness for final formulation (4-10) KP. So the result of the hardness tests satisfactory for the final formulation.

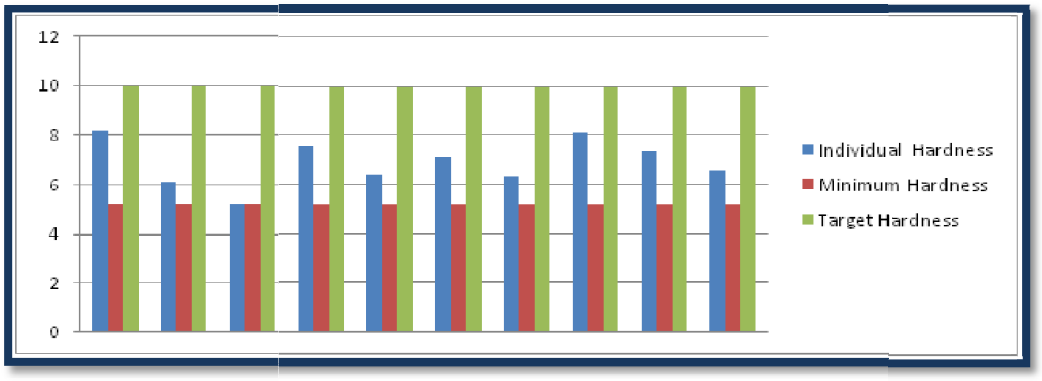


Figure 4.2. Hardness of 10 tablet of final formulation F-05

Table 2.8. Hardness of 10 tablet of final formulation F-06

Tablet serial No.	Individual hardness (Kp)	Maximum hardness (Kp)	Minimum hardness(Kp)	Average hardness(Kp)	Target hardness(Kp)
01	8.15	8.59	5.23	8.59	(4-10.00)
02	7.10				
03	5.23				
04	8.59				
05	6.36				
06	7.10				
07	6.32				
08	7.14				
09	7.32				
10	8.56				

Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. Two friability tests were performed for the final formulation F-05&F-06. The result of two formulation's friability test was within limit. The friability limit not more than 1% and two test shown satisfactory result that was shown by the table 2.7. The friability result of formulation F-06 showed relatively good result may be due to application of higher pressure to reduce thickness as well.

Table 2.9. Friability of 20 tablet after 100 Revolutions and 200 Revolutions of Formulation F-05 & F-06

Formulation	Friability	100 Revolutions	200 Revolutions	Target limit
F-05	Test-01	0.66%	0.97%	
	Test-02	0.56%	0.96%	
F-06	Test-01	0.45%	0.86%	Not more than 1%
	Test-02	0.44%	0.76%	

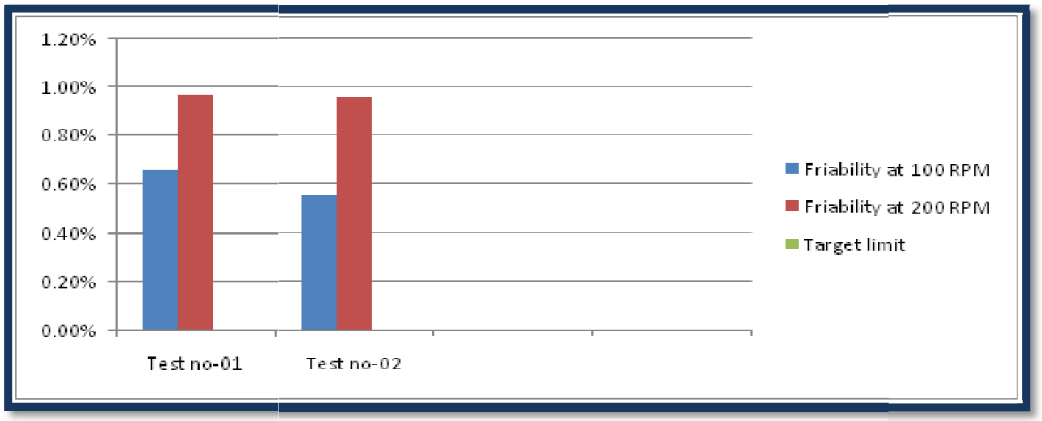


Figure 4.3. Friability test of formulation F-06

The disintegration test is performed to find out that within how much time the tablet disintegrates. This test is very important and necessary for all the tablets, coated or uncoated to be swallowed because the dissolution rate depends upon the time of disintegration which ultimately affects the rate of absorption of drugs. So the formulation F-05 showed disintegration time within limit according to the table no. 2.9. Formulations F-01 to F-04 were not considered for disintegration study due to poor tablet properties and rejected those formulations.

Table 2.10. Disintegration Time of Formulation F-05

Disintegration test	Disintegration time of formulation-05	Disintegration time specification (37˚c)
Test-01	6 Min 10 sec	NMT 15 min
Test-02	5 Min 4 sec	NMT 15 min
Test-03	4 Min 56 sec	NMT 15 min

Here the highest disintegration time shown by the test-01.All the test follow the specification limit (Not more than 15 Minutes) and represent a good formulation and also make perception that the product must be ensure good bioavailability. So, scope was still available to improve the quality**.** Formulation F-05 was then considered again to subject to disintegration test with the aim of providing good disintegration time than the previous one after controlling hardness and quantity of Magnesium stearate was slightly reduced as well as quantity of carmelose sodium was increased with reduction of final blending time of formulation F-05, which might ensure good dispersion of super disintegrant as well as reduction of lubrication which provided better disintegration time. This final formulation met the tablet specification also and represented a good formulation by ensuring good bioavailability followed by better disintegration time. Good disintegration time can be the pre-requisite of good dissolution property. This new changed process of formulation is denoted as formulation F-06.

Table 2.11. Disintegration Time of Formulation F-06

Disintegration test	Disintegration time of final formulation	Disintegration time specification (37˚c)
Test-01	4 Min 10 sec	NMT 15 min
Test-02	3 Min 58 sec	NMT 15 min
Test-03	4 Min 11 sec	NMT 15 min

Dissolution is the process by which a chemical or drug becomes dissolved in a solvent. The dissolution process occurs when solid particles or drug are in the GI tract, an essentially saturated solution of the drug builds up very quickly on the surfaces of the particles and in the liquid immediately

surrounding them. Dissolution was performed by USP apparatus-II (Paddle system) as per USP guidelines. The six points dissolution result of formulation F-06 is given below table no. 2.11.

Table 2.12. Release percentage of Epalrestat in 900ml after 45 min of formulation F-06

Test	Determined dissolution (%)	Specification of dissolution (≥70%)
Tablet-01	82.59	70
Tablet-02	82.02	70
Tablet-03	82.36	70
Tablet-04	82.22	70
Tablet-05	79.97	70
Tablet-06	80.55	70

The dissolution rate is one of the important parameter for the evaluation bioavailability of the tablet and the results of dissolution ensure the formulation show better efficacy.

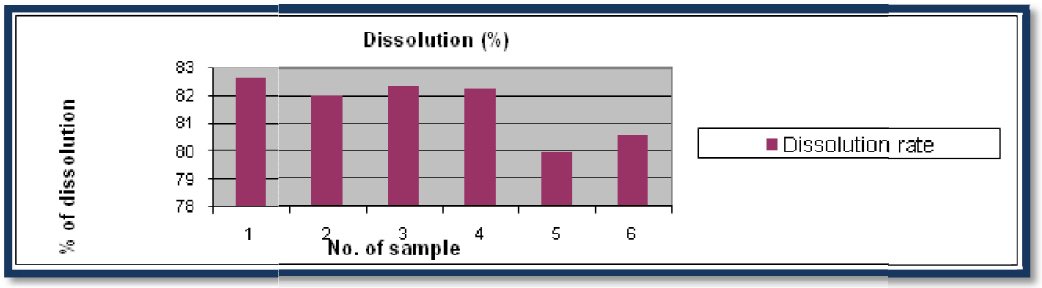


Figure 4.4. Dissolution rate of Epalrestat in 900ml after 45 min of formulation F-06

Assay content of formulation F-06 was performed by UV-Visible spectrophotometer .Epalrestat shows maximum absorbance at 400nm. So the absorbance of sample was detected at this wavelength .The concentration of sample 1mg/l. The assay result of Epalrestat tablet can be evaluated through spectrum peak report which can be ensured by the determination of Epalrestat Quantity through calculation as per USP guidelines. Here, three sample tested for the calculation of the assay of Epalrestat tablet. All the sample show good assay result. Because the stated potency of Epalrestat tablet in Monograph Not less than 90% and Not more than 110%.But the average assay result of three sample showed is 97.25% which met the specification.

Table 2.13. Assay result of tablets from formulation F-06

Test	Determined potency (%)	Lower limit that stated in monograph	Higher limit that stated in monograph
Sample-01	97.16	90.00	110.00
Sample-02	98.18	90.00	110.00
Sample-03	96.42	90.00	110.00

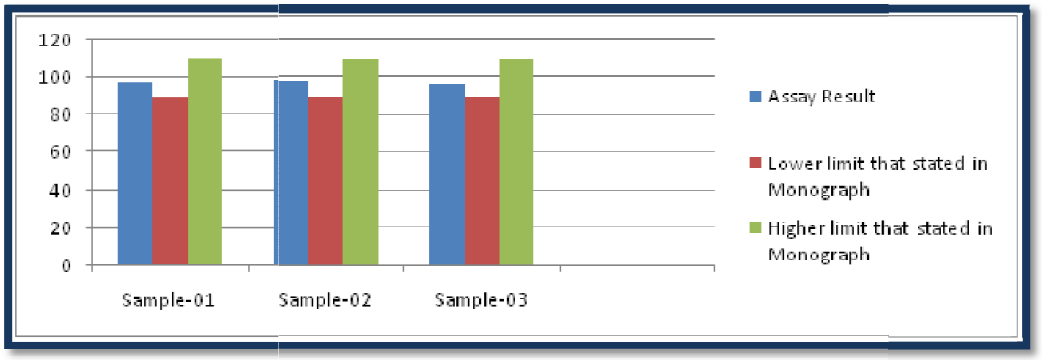


Figure 4.5. Assay result of formulation F-06 and comparison with stated potency in Monograph

Conclusion

Epalrestat is one of the most prominent drugs for the treatment of Diabetic neuropathy mostly for the treatment of peripheral diabetic neuropathy. Diabetic neuropathy is one of the leading disease conditions because of high percentage of people is now affected with this disease all over the world. Though symptomatic treatment of this disease is now prime concern but aldose reductase inhibitor (Epalrestat) is one of the new entry of weapons to fight against this silent killer to prevent the pathway to develop this painful condition[3]. In Bangladesh most of the people are not aware of their health condition so this disease in most case detected at the eleventh hour when almost all the probability to cure goes impossible. Though most of the people of Bangladesh lives below poverty line so, this dosage form can be the lead choice to formulated tablet of Epalrestat against Diabetic neuropathy.

Epalrestat is available in tablet dosage form by some local manufacturers of Bangladesh. This proposed formulation will provide better efficacy with low price due to cost effective measures have been taken during every steps of development. It is also noted by the performance of improved bioavailability specially parameter like lower Disintegration Time and greater Dissolution Rate. Other quality control tests (e.g. Thickness, Hardness, Friability, Individual Weight and content of active ingredients) were also performed to ensure its better tablet properties. The most amazing and attractive thing of my study is that the price will be cheaper than local

manufacturer of Bangladesh absolutely with better quality because of using some cheap but effective excipients which will help greatly for the poor in our country[7]. In addition, a further study can be done on the comparison of tablet properties including disintegration time and dissolution rate of this formulated tablets with other available market products to emphasize the statement of improved bioavailability with cheap rate with justified evidence[8-12].

References

1. Várkonyi T, Kempler P (2007). "Diabetic neuropathy: new strategies for treatment". *Diabetes, Obesity and Metabolism* 10 (2):1463-1326.
2. Saraswat, M.; Muthenna, P.; Suryanarayana, P.; Petrash, J. M.; Reddy, G. B. (2008). "Dietary sources of aldose reductase inhibitors: Prospects for alleviating diabetic complications". *Asia Pacific journal of clinical nutrition* 17 (4): 558-565.
3. Hotta N, Sakamoto N, Shigeta Y, Kikkawa R, Goto Y (1996). Clinical investigation of epalrestat, an aldose reductase inhibitor, on diabetic neuropathy in Japan: Multicenter study. *J Diabetes Compl*.10:168-72.
4. Uchida K, Kigoshi T, Nakano S (1995). Effect of 24 weeks of treatment with epalrestat: An aldose reductase inhibitor on peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *Clin Ther*.17:460-6. [*PubMed*].
5. Karen mitchell et.al (December 1990) .The influence of additives on the cloud point, disintegration and dissolution of hydroxypropyl methylcellulose gels and matrix tablets. *International journal of pharmaceutics* .66(1-3):233-242.
6. Manish Maladkar, Girish Rajadhyaksha, N. Venkataswamy, R. S. Hariharan, and Sathis R. Lohati (Jan-Mar, 2009). Efficacy, safety, and tolerability of Epalrestat compared to Methylcobalamine in patients with diabetic neuropathy, *Int J Diabetes Dev Ctries*.; 29(1): 28-34.
7. Raymond C R, Paul JS, Sian CO. Hand book of Pharmaceutical Excipients. 5th ed. London: Pharmaceutical Press and American Pharmacist association; 2006.
8. Z. T. Chowhan, (January 1998), Role of binders in moisture-induced hardness increase in compressed tablets and its effect on *in vitro* disintegration and dissolution, *Journal of Pharmaceutical Sciences*. 69(1): 1-4.
9. N. H. Shah, J. H. Lazarus, P. R. Sheth, C. I. Jarowski (June 1981). Carboxymethylcellulose: Effect of degree of polymerization and substitution on tablet disintegration and dissolution. *Journal of Pharmaceutical Sciences*, 70(6): 611-613.
10. Watanable Y. *et al* (2001), Preparation of rapidly disintegrating tablets using new type of MCC (PH-M-Series) and L-HPC by direct compression method, *Chemical pharm Bull*, 49(2):134-139.

11. Bi YX, Sunada H, Yonezawa Y, Danjo K (1999). Evaluation of rapidly disintegrating tablets prepared by a direct compression method. *Drug Dev Ind Pharm*. 25:571-581.
12. Fukami J., Yonemochi B., Yoshihashi Y., Terada K. S (2006). Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. *Int. J. Pharm*. 310:101-109.
13. Steele JW, Faulds D, Goa KL (1993). Epalrestat: A review of its pharmacology and therapeutic potential in late-onset complications of diabetes mellitus. *Drug Aging*. 3:532-55.