Original Article

Formulation And Evaluation Of Berberine Hydrochloride Film Coated Tablet

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Abstract

The purpose of the present study was to formulate and evaluate Berberine HCl Film coated tablet. Preformulation studies of API were done. The film coated tablets have advantages over conventional oral dosage forms, film coated tablet also influences the release of drug after compression. Film coating also help in making the tablet with good taste masking properties and excellent mechanical strength. It was revealed in the study that cellulosic coating materials were unable to resist the compression forces whereas hydroxypropyl methyl cellulose co-polymers resist the forces. Furthermore, aqueous dispersions of hydroxypropyl methyl cellulose co-polymers showed high flexibility as that of cellulosic materials thereby providing resistance from destructive compressional forces. The Preformulation characteristics were done as per the Pharmacopeial specifications. The drugs and excipients compatibility studies were carried out by FT-IR spectroscopy. Various pre-compressional parameters like bulk density, tapped density, compressibility index and Hausner's ratio and post-compressional parameters like weight variation, thickness, hardness, friability, disintegration time and drug release were studied. The spectra elucidate that there was no interaction between Drug and excipients. In order to achieve the best optimized product, five different formulations were developed using diluents, binder, glidant, lubricant, and different concentrations of super-disintegrant. The tablets were prepared by using wet granulation method. Optimization was done and it was found that release profile was found to be best with super-disintegrant that is Crospovidone and Enhance DT. Protectab HP-1 coating was done on Berberine HCl tablets. In-vitro release was carried out in medium 6.8 pH Phosphate buffer. The formulation F-5 was showed better drug release and selected as an optimized formulation.

Key words: Berberine Hydrochloride, DT, FT-IR, super-disintegrant, Film coated tablet.

1. INTRODUCTION

Tablets are defined as solid unit dosage form containing one or more active pharmaceutical ingredient and excipients with or without diluents used in the formulation of a complete preparation [1-3]. They are obtained by compressing uniform volumes of particles or by another suitable manufacturing technique, such as extrusion, moulding or freeze-drying (lyophilization) [4]. Some are swallowed whole, some after being chewed, dissolved in water before administration and some are retained in the mouth where the active substance is liberated [5-6]**.** Berberine (BER) is the most important active component of "*Rhizoma Coptidis"* which can be prepared from rhizomes of numerous herbs including "*Coptis chinensis"* French, "*Coptis deltoidea"* and "*Coptis teetoides"*. In about 500 A.D., the anti-diabetic activity of Rhizoma Coptidis was noted. On the other hand, in most books Rhizoma Coptidis is prescribed in the cure of infection and inflammation. Berberine is an OTC (over the counter) drug for the treatment of gastrointestinal infections, such as bacterial diarrhea [6-8]. The anti-diabetic effect of berberine was noted in 1988 in treating gastrointestinal infections patients with diabetes in China [9-14]. Berberine used as an anti-hyperglycemic agent by various physicians in China for several years, with many clinical reports on the hypoglycemic action of berberine [15-18]. However, berberine has low bioavailability (<5%) due to poor absorption. Diabetes is one of the earliest diseases to be known, and can be traced to 400 BCE where it was described by Indian physicians. Diabetes term was first used by the Greek Apollonius of Memphis in 230 CE. Effective treatments were not available until the Canadians Frederick Banting and Charles Best developed insulin in 1921 and 1922 [19-22]. According to data, there were 285 million people suffered with type-2 diabetes, about 90% of diabetes cases observed in 2011 [23-24]. In China, the incidence of diabetes is also high and is increasing; the incidence of diabetes in 2011 was estimated at 92.4 million adults with 43.01 million rural and 50.3 million urban patients. This high and increasing incidence of diabetes is supposed primarily to be due to worldwide population aging, less physical activities, smoking,

elevated cholesterol levels, high blood pressure, and increasing rates of obesity. In the majority of patients with type 2 diabetes, oral anti-diabetic drug treatment is the first-line treatment [25-27]. The most prescribed blood-glucose lowering agents, metformin, sulfonylurea and thiazolidinedione, may temporarily improve blood glucose control. Traditional Chinese medicine has the potential to give new candidates for the development of hypoglycemic drugs [28-30].

2. MATERIAL AND METHOD

2.1 MATERIALS

Berberine (API), EP/JP, IH, Indian Herbs Extraction, Crospovidone, USP, Kollidone-CL, Signet chemical corporation, Microcrystalline Cellulose, IP, Avicel-MCC -101, FMC Biopolymer, Povidone, IP, Stardone K-30, Star-tech and JRS specialty product Co. Ltd, Colloidal Silicon Dioxide, USP/NF, Aerosil, Mark Healthcare, Purified Talc, BP, Purified Talc, Signet chemical corporation Pvt. Ltd, Magnesium Stearate, USP/NF, Magnesium Stearate, Sudeep Pharma Pvt. Ltd, Croscarmellose sodium, Sodium starch glycolate, IP, Enhance DT, Bharat coats, Hydroxy propyl methyl cellulose, IP, Protectab HP1, Bharat coats.

2.2 METHODOLOGY

2.2.1 Preformulation Studies: Preformulation testing is a study of physiochemical properties of drug substance alone or with excipients. It is primary step in the development of dosage forms. The objective of pre-formulation testing is to make useful information to the formulator in developing stable and bioavailable dosage form which satisfy the essential properties of dosage form.

i) Physical Properties:

Melting Point: Capillary tube technique was used to find out the melting point of given API. In this technique drug was kept in capillary tubes, and temp measuring thermometer was also kept in melting point apparatus and the point at which drug was melted was noted.

Solubility Studies: The solubility testing was done to choose a suitable solvent system to dissolve the drug. Solubility drug was used to find out dispersion condition by the use of an excess amount of drug powder.

ii) Identification Study:

Measurement of λ_{max} by U.V. spectroscopy: The λ_{max} of Berberine was determined in a 100 ml of methanol. The solution was scanned in the range of 200-400 nm. The λ_{max} was found to be 345 nm with absorbance of 0.394.

Preparation of Stock Solution: The 10 mg drug was dissolved in 10 ml of methanol, which having concentration 1000 µg/ml. (stock solution)

Preparation of Dilutions: From the above stock solution dilutions were prepared in methanol and phosphate buffer (pH 6.8) respectively, having concentration 5, 10, 15, 20, 25, 30 µg/ml and observe the absorbance under UV-visible spectrophotometer (SHIMADZU 1700) at maximum wave length (λ_{max}) 345 nm and plot a calibration curve.

iii) Drug-Excipients Compatibility Studies by FTIR spectroscopy:

FTIR compatibility studies were performed to know the compatibility of the drug with other excipients. The KBr FTIR technique was used to observe the peaks of the sample. Thus, peaks obtained were give numerical value to know the compatibility between the drug and polymers which are to be used in the formulation. The instrument was calibrated by using polystyrene film. The drug powder was placed in IR compartment and scanned between wave number 4000^{-1}cm – 400 cm^{-1} using a Shimadzu Model 8400 FTIR, taking air as reference. [31-33]

2.2.2 Formulation and Development of Berberine Hydrochloride Film Coated Tablet:

For preparing the uncoated tablet weigh all the given excipient according to their quantity. Shift Berberine Hydrochloride, Micro-crystalline cellulose and crospovidone through #40. Transfer the sifted material of into a polyethylene bag and mix for 10 minutes. Take 242 gm. of Purified in a beaker. In 240 gm. of Purified water add 3.5 gm of Polyviny Pyrrolidone K-30 with continuous stirring. Mix solution properly until a lumps free solution is obtained and keeps aside remaining quantity (2.00 gm.) of Purified water. Add binder solution of above step to the dry mix blend and mix for 10 minutes. Complete granulation by adding remaining quantity of Purified water (2.00 gm.), if required. Mix the blend for 5 minutes. Load the wet granules of in the Hot air oven and dry the wet granules for 5 minutes. Further dry the granules at temperature 60°C for 20-40 minutes or till the LOD of the granules are achieved 3.00% to 5.00% w/w.

Pass the dried granules of through #20 sieves. Check the lubricating ingredients for their quantity and sift the material and collect in a polyethylene double lined container separately**.** Load the sized granules of stage into the blender. Mix the content for 3 minutes at slow speed. Add the shifted lubrication and blend for 5 minutes at slow speed. Fix 16.5 x 8.0 mm capsule shaped, concave punch with break line and dies for the corresponding punches. Transfer the blend of in the hopper and adjust to set the fill weight to **720.00 mg** per tablet. Collect the tablets in labeled containers lined with double polyethylene bags. Weigh the ingredients and take 14.00 gm. of Protectab HP 1 into the beaker and add required quantity

of purified water into it under continuous stirring. Clarify the slurry through #100 mesh sieve. De-dust the tablets and load them in the coating pan. Start the coating process with coating solution and check for In-process control. On completion of Coating operation, dry the tablets for 10-15 minutes at 40-60°C and allow rolling for 5 minutes. [34]

2.2.3 *In-vitro* dissolution test:

Preparation of 0.1N Hydrochloric acid: Mix 59.6 ml of concentrated hydrochloric acid in 7000ml of purified water.

Standard Preparation: Weigh accurately about 100 mg of Berberine Hydrochloride Working Standard into a 100 ml volumetric flask further 2ml in 100 make up the volume with mobile phase and mix well. Filter the solution using 0.45µ membrane filters.

Sample Preparation: Keep 6 bowls in dissolution apparatus with 900 ml of 0.1 N HCl dissolution media. After obtaining the required temperature, place one tablet in each bowl and start the rotation. Collect 10 ml of sample after each time interval and filter through Whattman filter paper no. 42, by discarding first few ml of filtrate. After each withdrawal, sample was replaced with 10 ml of media.

Procedure:

1. Dissolution study of tablet performed in USP II (paddle) dissolution test apparatus using 900 ml of 0.1 N HCl as a dissolution media.
2. The tablet was loaded into an each basket of dissolution apparatus; the temperature of dissolution media was maintained at 37°C ± 0.5^0C with stirring speed of 75 rpm throughout the study.
3. Aliquots of dissolution media containing 10 ml of samples were withdrawn at time interval of 10, 15, 20, 30, and 45 minutes and 10 ml of fresh dissolution media maintained at the same temperature was replaced after each withdrawal.
4. Examine and note the absorbance of sample and standard preparation at the maximum at about 345 nm. [35]

2.2.4 Test for Assay:

Chromatographic Conditions:

Column: C18, 250 × 4.0 mm, 5µm octadecylsilanized silica gel.
Flow rate: 1.5 ml/minute
Wavelength: 345 nm
Column temperature:40°C±2°C
Injection Volume : 10µl
Retention time: Palmatin chloride about 10 minutes
Run time: about 2 time of retention time of berebrine hydrochloride.

Preparation of Diluent: Mixture of Water: Acetonitrile (1:1). Take 50 volumes of HPLC grade water and 50 volumes of Acetonitrile mix and degas it.

Preparation of Mobile Phase: Weigh about 3.4 g of monobasic potassium phosphate and 1.7 g of sodium lauryl sulphate and dissolve in 1000 ml diluents and filter the solution through 0.45 µ membrane filter paper.

Preparation of Standard solution:

1. Weigh accurately about 100 mg of Berberine Hydrochloride reference/working standard transfer in to a 100 ml of volumetric flask add 40 ml of mobile phase, sonicate to completely dissolve and make the volume up to the mark with mobile phase.
2. Dilute 5 ml of above solution transfer into 50 ml volumetric flask add 30 ml of mobile phase and make up the volume up to the mark with mobile phase and filter through 0.45µ membrane filter paper. Discard first few ml of filtrate.

Resolution standard solution: Weigh accurately about 1.0 mg of Berberine Hydrochloride and 1.0 mg of Palmatin Chloride reference/working standard transfer in to a 100 ml of volumetric flask add 10 ml of mobile phase, sonicate to completely dissolve and make the volume up to the mark with mobile phase.

Preparation sample solution: Take the 20 tablets randomly and crushed into the fine powder with mortar pestle. Weigh accurately about 150.0 mg of tablet powder (equivalent to 100 mg of Berberine Hydrochloride) transfer in to a 100 ml of volumetric flask add 40 ml of mobile phase, sonicate to completely dissolve and make the volume up to the mark with mobile phase. Filter the above solution through 0.45µ membrane filter paper discard the few ml of filtrate solution. Pipette out the 5 ml of filter solution transfer into 50 ml of volumetric flask and make the volume up to the mark with mobile phase and mix.

Procedure: Separately inject 10 µl inject the solutions in the following sequence into the Chromatographic, record the chromatograms and measure the response for major peak. [36, 37]

3. RESULT AND DISCUSSION

3.1 Measurement of λ_{max} by U. V. spectroscopy:

The λ_{max} of Berberine Hydrochloride was found to be 345 nm, and absorbance was found to 0.795 nm in methanol. Preparation of Calibration Curve of Berberine Hydrochloride in different medium (phosphate buffer pH 6.8 and 0.1N HCl)

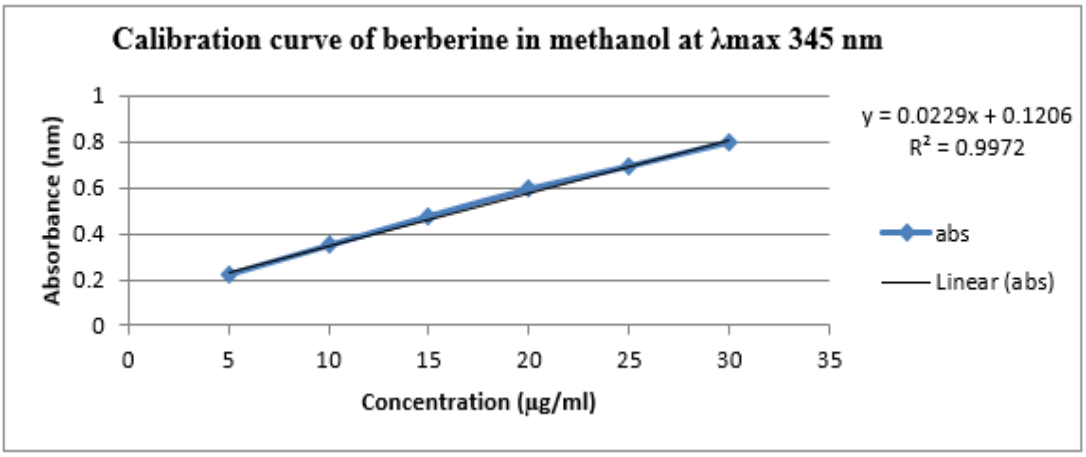

Figure 1: Calibration curve of Berberine in methanol

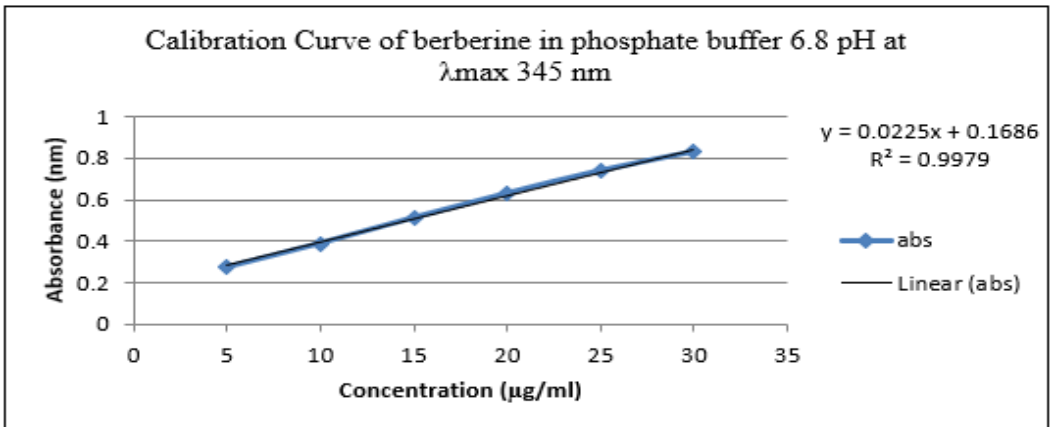

Figure 2: Calibration Curve of Berberine in Phosphate buffer pH 6.8

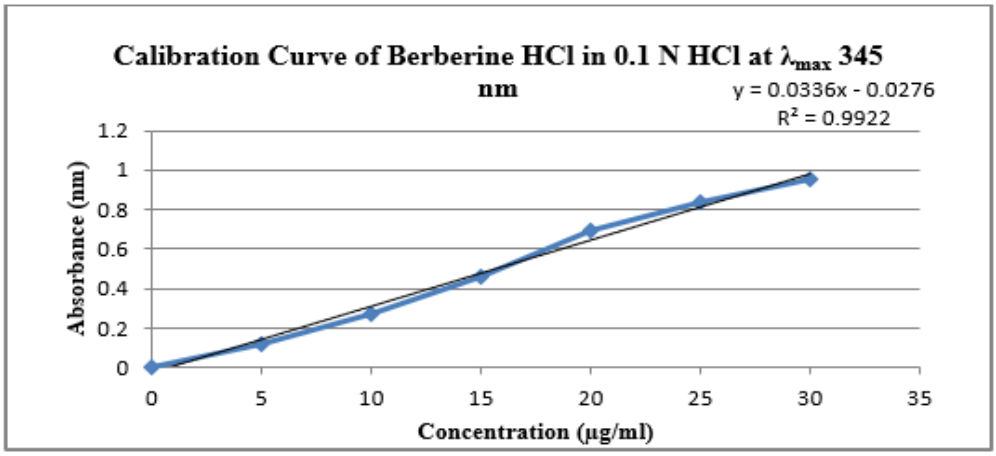

Figure 3: Calibration Curve of Berberine HCl in 0.1 N HCl

3.2 Solubility study: Berberine HCl sparingly soluble in methanol; slightly soluble in Ethanol (95%) and very slightly soluble in water.

Table 1: Solubility study of drug in different solvents

S. No.	Solvents	Solubility
1	Methanol	Sparingly soluble

2	**Ethanol (95%)**	**Slightly soluble**
3	**Water**	**Very slightly soluble**

3.3 Physical property: (API Characterization (Berberine Hydrochloride))

- ***Color-****Yellow in color,*
- ***Taste-****Bitter in Taste*
- ***Odour-****Characteristics*

3.4 Analytical Evaluation:

UV-Analysis: The standard curve of Berberine hydrochloride was carried out in water and scanned for wavelength 200 – 400 nm. Spectra observed at λ_{max} 345 nm.

Standard curve of Berberine hydrochloride in phosphate buffer 6.8 pH

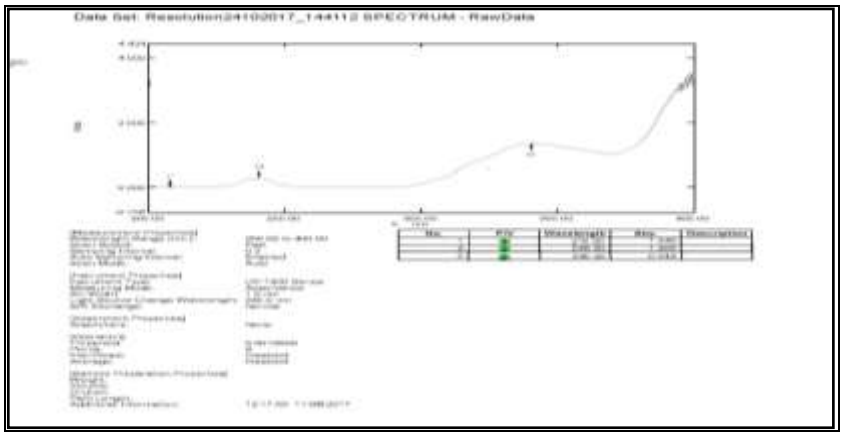

Figure 4: Peak for finding λ_{max} of Berberine hydrochloride in phosphate buffer pH 6.8

Table 2: Drug – Excipients Compatibility study by FTIR

S. No	Name of the Ingredients	Ratio	Remarks
1.	API	1:0	-
2.	API + crospovidone	1:1	Compatible
3.	API + MCC	1:1	Compatible
4.	API + Aerosil	1:1	Compatible
5.	API + magnesium stearate	1:1	Compatible
6.	API + povidone	1:1	Compatible
7.	API + Talc	1:1	Compatible

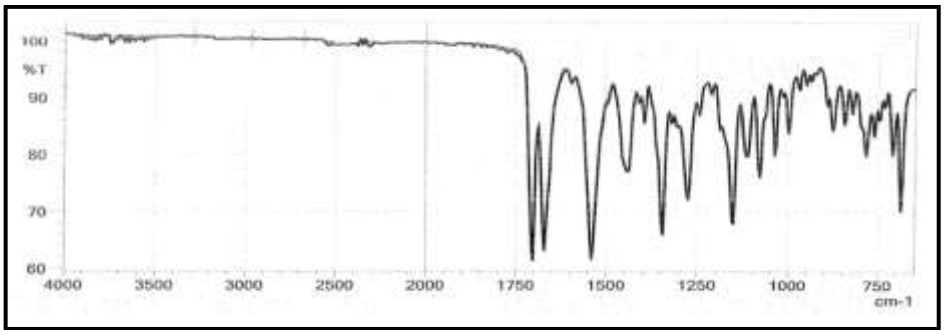

Figure 5: Fourier transform infra-red spectrometry of Berberine HCl

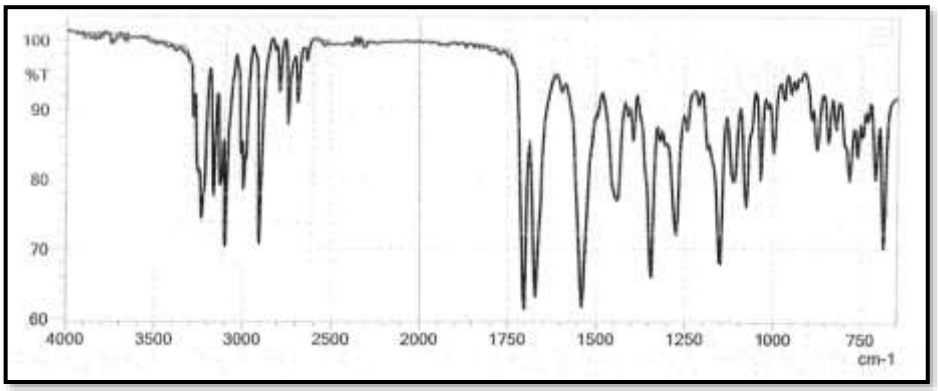

Figure 6: Fourier transforms infra-red spectrometry of Berberine + Crospovidone

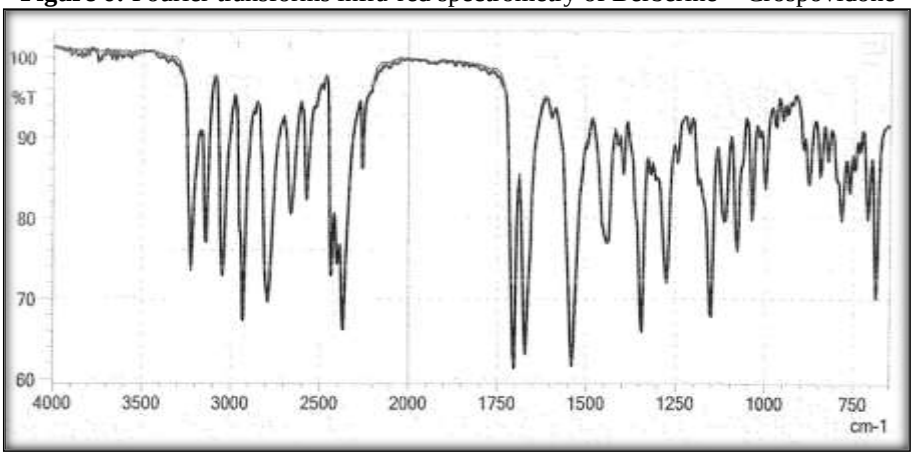

Figure 7: Fourier transform infra-red spectrometry of Berberine + MCC

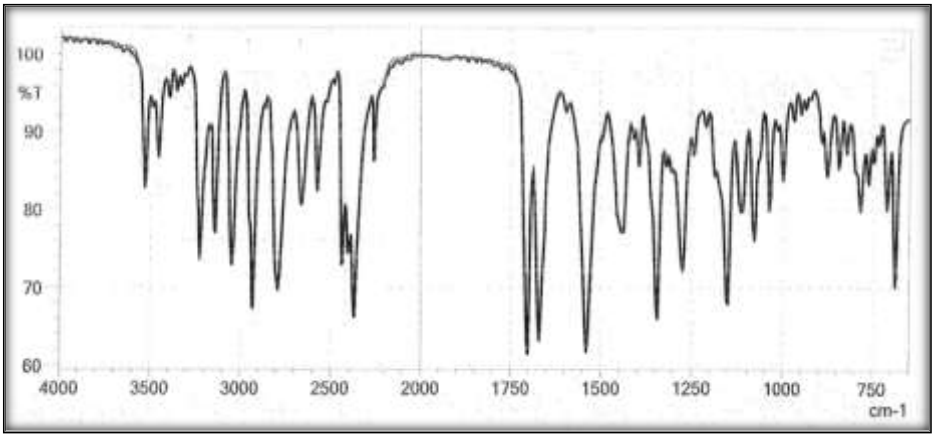

Figure 8: Fourier transform infra-red spectrometry of Berberine + PVP K- 30

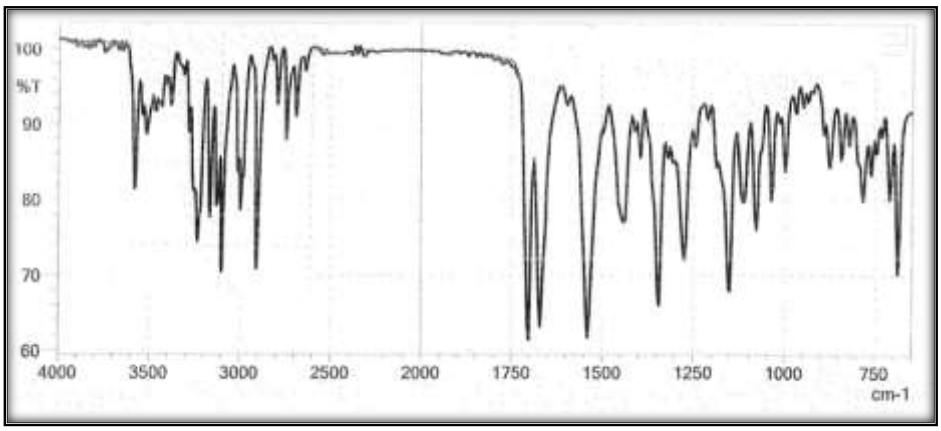

Figure 9: Fourier transform infra-red spectrometry of Berberine + Aerosil

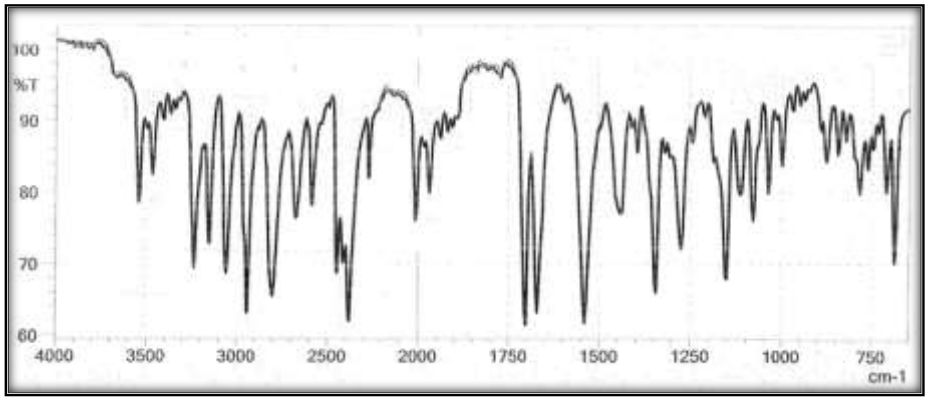

Figure 10: Fourier transform infra-red spectrometry of Berberine + Talc

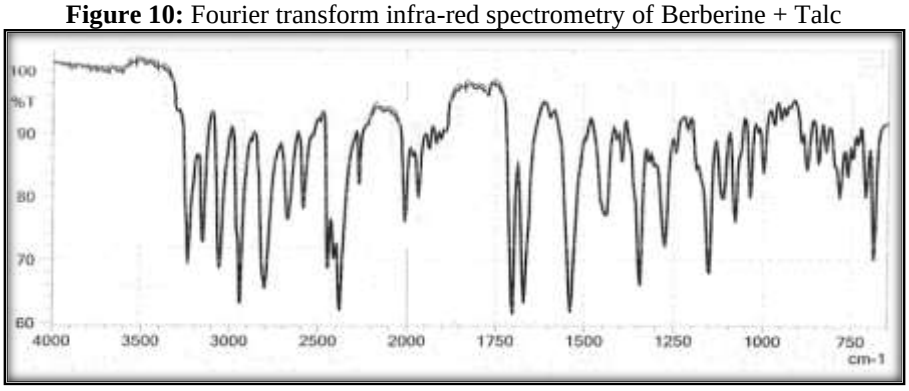

Figure 11: Fourier transforms infra-red spectrometry of Berberine + Magnesium Stearate

3.5 Formulation and Development of Berberine Hydrochloride Film Coated Tablet: Formulation chart mention in table 3.

Table 3: Composition of Berberine Hydrochloride Film Coated Tablet

S. No	Ingredients	F1	F2	F3	F4	F5	F6
		Quantity mg/tablet					
	Intra-granular Material						
1.	Berberine HCl	552.5	552.5	552.5	552.5	552.5	552.5
2.	SSG	20	30	40	--	--	--
3.	Crospovidone	--	--	--	30	35	35
4.	MCC-101	126.5	98.5	78.5	81.5	76.5	76.5
	Composition of Binder solution						
5.	PVP K-30	--	10	10	7	7	7
6.	Purified water	--	qs	q.s	q.s	q.s	q.s
	Lubrication Material						
7.	Crospovidone	--	--	10	--	--	--
8.	Aerosil	7	10	10	10	10	10
9.	Enhance DT	--	--	--	20	20	20
10.	Talc	10	14	14	14	14	14
11.	Magnesium stearate	4	5	5	5	5	5
Weight of core tablet		**720.00**	**720.00**	**720.00**	**720.00**	**720.00**	**720.00**
12.	Protectab HP1	--	--	28.00	28.00	28.00	28.00
13.	Purified water	--	--	q.s	q.s	q.s	q.s
Weight of coated tablet		**--**	**--**	**748.00**	**748.00**	**748.00**	**748.00**

3.6 Evaluation Of Pre-Compression Parameters Of Powder Blend Of All Formulation: Various precompression parameter mention in table 4.

Table 4: Evaluation of Pre-compression Parameter

Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Angle of repose (θ)	Hauser's ratio
F-1	0.385	0.558	25.15	36.56	1.44
F-2	0.425	0.521	23.29	34.15	1.22
F-3	0.523	0.612	20.45	28.13	1.17
F-4	0.339	0.502	20.11	30.63	1.25
F-5	0.494	0.648	1.83	28.97	1.17
F-6	0.557	0.654	14.83	28.97	1.17

3.7 Evaluation of Post-Compression Parameters of Tablet of All Formulation: Evaluation parameter mention table 5 and 6.

Table 5: Evaluation of Post Compression Parameters of Uncoated tablet

Formulations	Average Weight (mg)	Average Thickness (mm)	Average Hardness (kg/cm^2)	Friability (%)	Disintegration time (min)
F-1	718.48	5.19	10.54	0.85	21:02
F-2	719.52	4.65	12.33	0.58	24:10
F-3	719.00	5.21	10.86	0.52	15:10
F-4	720.56	5.72	14.15	0.42	14:05
F-5	719.25	4.81	13.45	0.19	11:12
F-6	720.55	4.81	13.45	0.19	11:12

All data was taken with average of 20 tablets.

Table 6: Evaluation of Post Compression Parameters of Coated tablet

Formulations	Average Weight (mg)	Average Thickness (mm)	Disintegration time (min)
F-1	745.48	6.89	ND
F-2	742.52	6.75	ND
F-3	740.88	6.88	18:25
F-4	747.56	6.72	15:22
F-5	748.55	6.81	12:05
F-6	748.55	6.81	12:05

Table 7: Test for Assay

Formulation	F3	F4	F5	F6
Assay in %	93.17	93.92	96.5	96.2

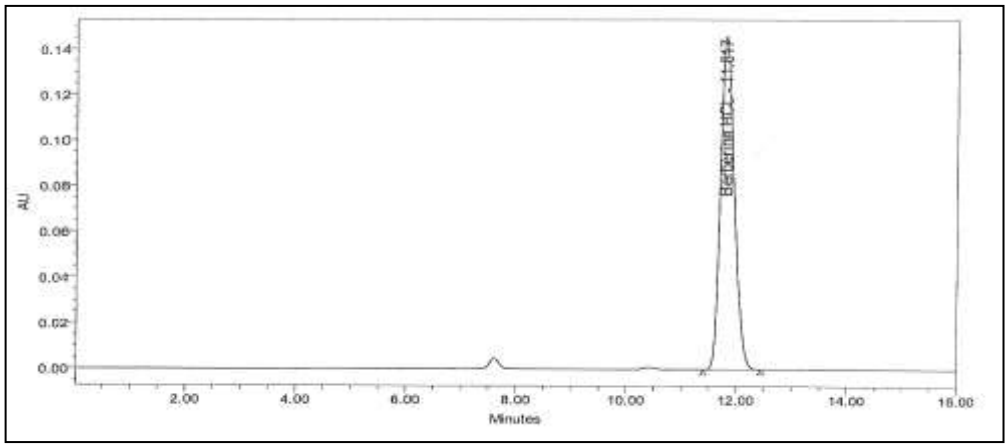

Figure 12: Spectrum peak of standard sample of Berberine Hydrochloride

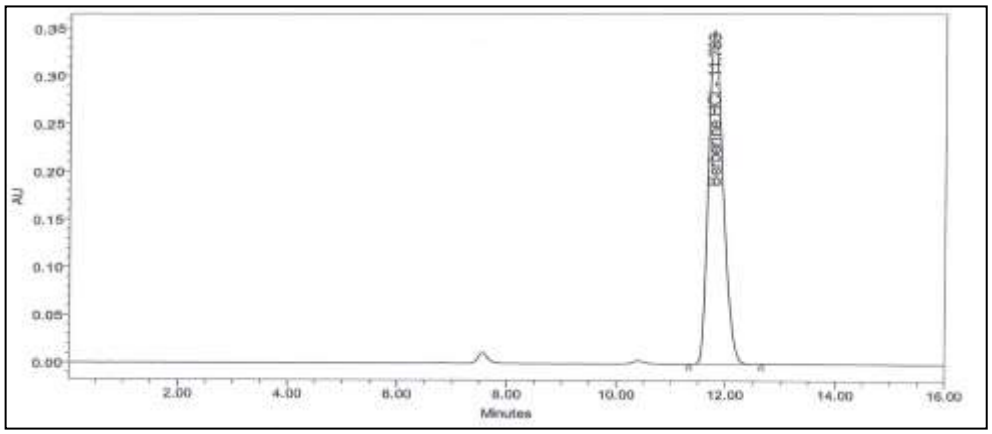

Figure 13: Spectrum peak of formulation sample (F-3) of Berberine Hydrochloride

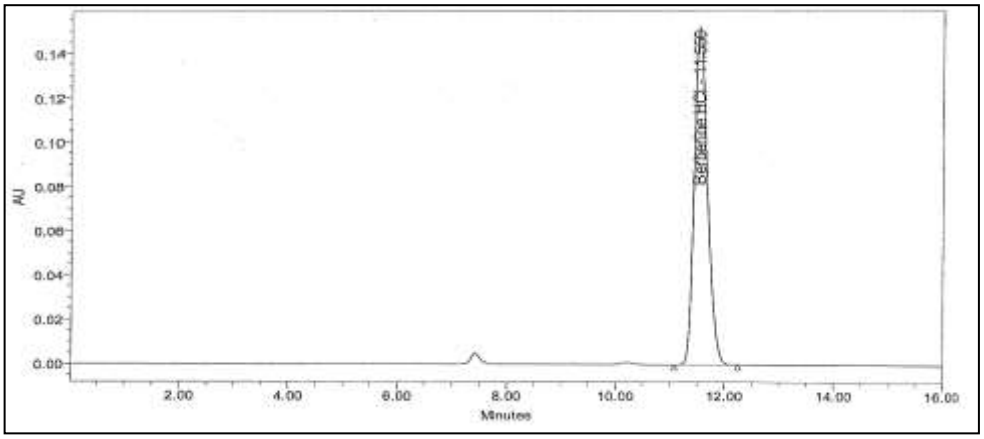

Figure 14: Spectrum peak of standard sample (F-4) of Berberine Hydrochloride

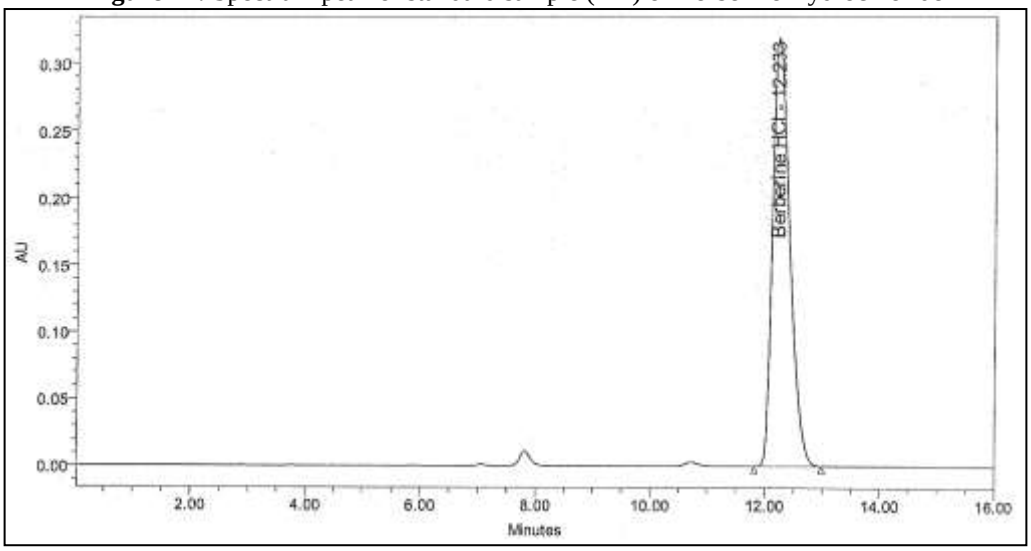

Figure 15: Spectrum peak of formulation sample (F-6) of Berberine Hydrochloride

3.8 *In-vitro* Drug Release Study of All Formulations in 0.1 N HCl: In-vitro drug of berberine HCl film coated tablets mention in figure 16.

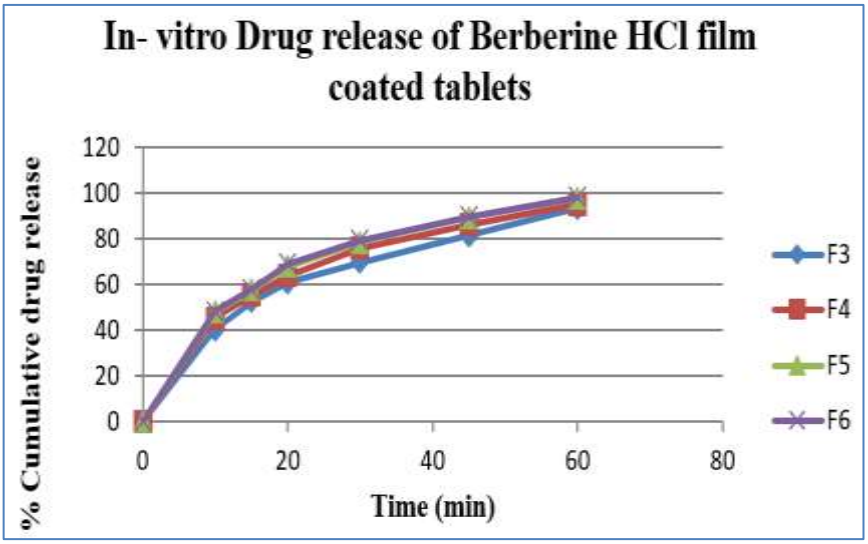

Figure 16: % Drug release of film coated tablet of Berberine HCl

3.9 DISCUSSION

The main objective and discussion of this study is to develop film coated tablet of Berberine Hydrochloride which is a herbal drug and have less side effects. Those who are suffered from Diabetes Mellitus type –II. Diabetes mellitus type-II is one of the earliest diseases to be recognized and can be traced to 400 BCE where it was described by Indian physicians. The need of this study is to select excipients which can show a good compatibility and stability study with API. Pre-

formulation studies of drug like loss on drying, melting point, bulk characterization, Optimization of the formula & composition of Berberine hydrochloride film coated tablet were also take in consideration to make a formulation therapeutically effective and stable. Berberine is an anti-hyperglycemic agent. Berberine is characterized as an AMP-activated protein kinase activator. Activation of AMPK is identified to increase insulin sensitivity and regulate mitochondrial function. After exposure to Berberine tablet AMPK phosphorylation was increased from 0.5 h and maintained approximately 16 hours in cells. The outcomes approve that an oval-shaped film-coated dosage form enhances the ease of swallowing for patients, enabling the dosage to quickly pass through the esophagus, without unease mucosal irritation. Coated oval tablets seem most likely to provide greater patient comfort, acceptance and safety, and could also lead to enhanced patient choice for a medication in this form. The preparation method of the Berberine Hydrochloride tablet is wet granulation method. F1 was prepared by the direct compression method, blend exhibit the poor flow characteristics. F2 was prepared by the slugging process, blend exhibit passable flow characteristic and disintegration time is very high that's why coating was not done. F3 and F6 prepared by the wet granulation process, the blend exhibit the good flow characteristics. In vitro release study of various formulations was done. All the formulation (F3 to F6) of tablet was study for 60 minutes. Among these formulations, the formulation **F6 showed highest drug release (98.1%) in 60 minutes,** and F3 showed least drug release (93.3) at the end of 60 minutes. As per the *in-vitro* studies it indicates that the F6 formulation was shows best drug release.

4. CONCLUSION

Berberine HCl film coated tablets were prepared by wet granulation method. The formulations F1, F2, F3, F4, F5 and F6 were prepared and all evaluation parameters were evaluated. The Weight variation, hardness, thickness and friability disintegration times for the formulated tablets are within the range of USP limit. Optimization was done and it was found that release profile was found to be best with super-disintegrants i.e. Crospovidone and Enhance DT. Film coating of Protectab HP-1 was done on Berberine Hydrochloride tablets as to avoid the humidity. The Percentage cumulative drug release of F6 was found at 60 Minutes 98.1%. The film coated tablets have advantages over conventional oral dosage forms, film coated tablet also influences the release of drug after compression. Film coating also help in making the tablet with good taste masking properties and excellent mechanical strength. It was revealed in the study that cellulosic coating materials were unable to resist the compression forces whereas hydroxypropyl methyl cellulose co-polymers resist the forces. Furthermore, aqueous dispersions of hydroxypropyl methyl cellulose co-polymers showed high flexibility as that of cellulosic materials thereby providing resistance from destructive compressional forces. The aqueous dispersions because of their flexibility attain the deformed shape of tablet and thus preventing damage to the coating. The coated tablet at high concentration of coatings increases the resistance to compressional changes.

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7. CONFLICT OF INTEREST:

There is no conflict of interest.

8. REFERENCES

1. Maghrabia AE, Boughdady MF, Meshali MM. New perspective enteric-coated tablet dosage form for oral administration of ceftriaxone: in vitro and in vivo assessments. AAPS Pharm Sci Tech, 2019; 20(7): 1-12.
2. Luo A, Fan Y. Antioxidant activities of berberine hydrochloride. Journal of Medicinal Plants Research, 2011; 5(16): 3702-3707.
3. LI J, LIU DX, MA QL. Preparation and Quality Control of Berberine Hydrochloride Colon-specific Enteric-coated Tablets. Food and Drug. 2007.
4. Zhu JX, Tang D, Feng L, Zheng ZG, Wang RS, Wu AG, Duan TT, He B, Zhu Q. Development of self-microemulsifying drug delisvery system for oral bioavailability enhancement of berberine hydrochloride. Drug Development and Industrial Pharmacy, 2013; 39(3): 499-506.
5. Li G, Zhao M, Su X, Song L, Zhao L. Preparation and in vitro-in vivo evaluation of intestinal retention pellets of Berberine chloride to enhance hypoglycemic and lipid-lowing efficacy. Asian Journal of Pharmaceutical Sciences, 2019; 14(5): 559-568.
6. Zhou HY, Cao PP, Zhao J, Wang ZY, Li JB, Zhang FL. Release behavior and kinetic evaluation of berberine hydrochloride from ethyl cellulose/chitosan microspheres. Frontiers of Materials Science. 2014; 8(4): 373-82.
7. Zhang Y, Cui YL, Gao LN, Jiang HL. Effects of β-cyclodextrin on the intestinal absorption of berberine hydrochloride, a P-glycoprotein substrate. International journal of biological macromolecules, 2013; 59: 363-371.
8. Singh IP, Mahajan S. Berberine and its derivatives: a patent review (2009–2012). Expert opinion on therapeutic patents, 2013; 23(2): 215-231.
9. Wang C, Perumalla SR, Lu R, Fang J, Sun CC. Sweet berberine. Crystal Growth and Design, 2016; 16(2): 933-939.
10. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism, 2008; 57(5): 712-717.
11. Pang B, Zhao LH, Zhou Q, Zhao TY, Wang H, Gu CJ, Tong XL. Application of berberine on treating type 2 diabetes mellitus. International journal of endocrinology, 2015.
12. Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evidence-based complementary and alternative medicine, 2012.
13. Dharmananda S. New uses of berberine. A Valuable Alkaloid from Herbs for "Damp Heat" Syndromes, 2005.
14. Gupte S. Use of berberine in treatment of giardiasis. American Journal of Diseases of Children, 1975; 129(7): 866-866.
15. Tang J, Feng Y, Tsao S, Wang N, Curtain R, Wang Y. Berberine and Coptidis rhizoma as novel antineoplastic agents: a review of traditional use and biomedical investigations. Journal of ethnopharmacology, 2009; 126(1): 5-17.
16. Fonner DE, Anderson NR, Banker GS. Granulation and tablet characteristics. In Pharmaceutical Dosage Forms: Tablets Vol. 2 Edited by H. Lieberman and L. Lachman. Dekker, New York, 1982, 202
17. Tung NT, Nguyen CH, Nguyen VD, Nguyen THT, Nguyen VL, Tran CS, Pham TMH. Formulation and in vivo imaging evaluation of colonic targeting tablets prepared by a simple dry powder coating technique. Journal of Pharmaceutical Investigation, 2020; 50(4): 383-398.

18. Li G, Zhao M, Su X, Song L, Zhao L. Preparation and in vitro-in vivo evaluation of intestinal retention pellets of Berberine chloride to enhance hypoglycemic and lipid-lowing efficacy. Asian Journal of Pharmaceutical Sciences, 2019; 14(5): 559-568.
19. Lee YS, Kim WS, Kim KH. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes. 2006; 55: 2256–64
20. Jayaprakasam B, Olson LK, Schutzki RE. Amelioration of obesity and glucose intolerance in high-fat-fed C57BL/6 mice by anthocyanins and ursolic acid in Cornelian cherry (Cornus mas) J Agric Food Chem. 2006; 54: 243–8
21. Matsui T, Ueda T, Oki T. alpha-Glucosidase inhibitory action of natural acylated anthocyanins. 2. alpha-Glucosidase inhibition by isolated acylated anthocyanins. J Agric Food Chem. 2001; 49: 1952–6.
22. Yin J, Gao Z, Liu D. Berberine improves glucose metabolism through induction of glycolysis. Am J Physiol Endocrinol Metab. in press.
23. Matthews DR, Hosker JP, Rudenski AS. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28: 412–9.
24. Ni YX. Therapeutic effect of berberine on 60 patients with type II diabetes mellitus and experimental research. Zhong Xi Yi Jie He Za Zhi. 1988; 8: 711–3. 707.
25. DeFronzo R, Goodman A. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med. 1995; 333: 541–9.
26. Ceriello A, Johns D, Widel M, et al. Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postload glycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. Diabetes Care. 2005; 28: 266–72.
27. Zhou L, Yang Y, Wang X, et al. Berberine stimulates glucose transport through a mechanism distinct from insulin. Metabolism. 2007; 56: 405–12.
28. Gao CR, Zhang JQ, Huang QL. Experimental study on berberin raised insulin sensitivity in insulin resistance rat models. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1997; 17: 162–4
29. Yin J, Ye J, Jia W. Effects and mechanisms of berberine in diabetes treatment. Acta Pharmaceutica Sinica B, 2012; 2(4): 327-334.
30. Khin-Maung U, Nyunt-Nyunt-Wai AK. Clinical trial of berberine in acute watery diarrhoea. British medical journal (Clinical research ed.), 1985; 291(6509): 1601.
31. Parmar KD, Bhatt NM, Pathak N, Chauhan Vijay V, Patel LD, Kela AN, Nathani HS. An Overview: Aqueous Film Coating Technology on tablets. Int J Pharm. and chem. science 2012; 1(3): 06-07.
32. Pole S, Maurya S, Hanale P. Rathod N, Bendale S, Khutle NM. A detail understanding of enteric coated tablet: manufacturing and evalution. Eur J Pharma Med Res. 2016; 3(4): 13-44.
33. Bagadde O, Pujari R, Nemlekar NA, Kharat PP. Appraisal On: Tablets Coating and its outcome with complementary Sprouting technology. Res J Pharm Biol Chem Sci Apprais. 2014; 5(5): 298-315.
34. Sharma P, Khinchi MP, Chetan Dubey PS. Recent advancement in tablet coating technology. World J Pharm Pharm Sci. 2017; 6(4): 2189-204.
35. Mounica P, Pavani S, Mounica PR. a review on recant advances in enteric coating and enteric polymers. World J Pharm Res. 2018; 7(2): 475-95.
36. Ankit G, Ajay B, Kumar KM, Neetu K. tablet coating techniques: concept and recant trends Gupta Int. Res J Pharm 2014; 4(2): 50-8.
37. Himaja V, Sai Koushik O, Srinivasa Babu P, Karthikeyan R, a Comprehensive Review on tablets coating, Austin Pharmacol Pharm 2016; 1(1): 1-8.