Research Article

Efficacy of Preparation of Time Programmed Double Pulse Press Coated Tablet containing Fixed Dose Combination of Montelukast Sodium and Levocetrizine dihydrochloride for Treatment of Nocturnal Asthma

Nidhal Khazaal Maraie*, Anmar Abdel Razzaq Albahadily
Pharmaceutical department, college of pharmacy, Al-mustansiriya University, Iraq.
***Corresponding author's E-mail:** pharm.dr.nidhal.khazaal@uomustansiriyah.edu.iq

Accepted on: 10-11-2016; **Finalized on:** 30-11-2016.

ABSTRACT

Chronotherapy systems (Pulsatile delivery systems) are non-conventional dosage forms designed to release the active ingredient after a lag time according to circadian rhythm of disease states. Asthma show typical circadian pattern. 80% of nocturnal asthmatic attacks occur between midnight and 8 a.m., and deaths from asthma are more common during these 9 hours. The aim of the work is to formulate montelukast sodium and levocetrizine dihydrochloride as chrono therapeutics (double pulse release) tablet to treat and relieve symptoms of asthma and nocturnal asthmatic attack at early morning. This is achieved through preparation of core tablet contain montelukast sodium, core tablet containing 10 mg of montelukast sodium was prepared with various types and concentrations of superdisintegrants. The best core tablet formula (containing 5% of cross carmellose) gave 100 % release of montelukast sodium within five minutes. Then selection of best coat layer in order to be pressed on the core tablet to get press coated core tablet was prepared and optimized through using different polymers used to get the best lag time (6hrs) as required . Two best coating layer were chosen containing combination of HPMC k4m with spray dried lactose and combination of HPMC k4m and EU L100.Finally the outer layer containing levocetrizine 2HCl (5 mg) with cross carmellose as super disintegrant in different concentrations for optimization. The best outer layer compressed to enclose the prepared coated tablet and to give 100% release of levocetrizine dihydrochloride within five minutes.

Keywords: Pulsatile, asthma, montelukast sodium, HPMCk4m, and levocetrizine dihydrochloride.

INTRODUCTION

A biological rhythm is mechanism for keeping normal body organs activity throughout sleep-wake cycle and it may be short (take seconds) like heart beat and nervous system impulses, normal (occur during 24 hrs.) like hormones and enzyme secretions, or long (take months) like menstrual cycle.[1] A diurnal rhythm in the occurrence and severity of asthma symptoms is almost universal with disturbed sleep due to enhanced symptoms at night paralleled by a change in lung function.[2] The onset of nocturnal asthmatic attacks occurs between midnight and 8 a.m., and deaths from asthma are more common during these 9 hours.

Pulsatile dosage form one of application of modified release dosage forms in which the drugs release at predetermined time, i.e. pulsatile drug release is such a system where drug released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug released from the device within this lag time.[3]This dosage form can provide one or more rapid release pulses at programmed lag times which results in better absorption of the active substance, thus provide an effective plasma peak.[4]

Montelukast sodium is a selective leukotriene receptor antagonist used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies. Levocetrizine dihydrochloride is an orally active R-enantiomer of cetirizine and is a third generation,non-sedating selective peripheral H1-receptor antagonist displacing histamine induced bronchoconstriction.[5] Due to incompatibility between montelukast sodium and levocetrizine dihydrochloride when combined together in a single unit tablet.[6] Therefore, bilayer tablets were reported to prepare each layer containing one of these drugs.

The aim of present work is to develop and evaluate double pulse time programed press coated tablet containing fixed dose combination of montelukast (10 mg) and levocetrizine (5 mg) intended for chronotherapy of asthma disease, where the first pulse involve rapid release of levocetrizine followed by 2nd pulse after 6 hrs lag time involving rapid release of montelukast. This may provide maximum plasma concentration of both drugs at time of its maximum need, in addition to providing stability for both drugs in the same tablet.

MATERIALS AND METHODS

Preparation of Inner Layer (Core Tablet)

Different powder blends of core layer which contain montelukast sodium as active ingredient with different types of super disintegrants and different types of diluents were prepared to be evaluated for their flow properties and compressibility before compressing into tablet using direct compression method as shown in table 1.

Selection of Coating Layer for the Prepared Core Tablet

Different types of polymers and polymers combination used to coat the core tablet in order to get the appropriate lag time (6 hours).

Table 1: Composition of Core Tablet

Ingredients	F1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
Montelukast sodium (mg)	10	10	10	10	10	10	10	10	10	10
Avicel (mg)	23.6	23.25	23.1	22.9	22.7	22.5	22.2	20.4	22.2	22.2
Croscarmellose(mg)	0.35	0.7	0.87	1.05	1.22	1.4	1.75	3.5	-	-
Sodium starch Glycolate (mg)	-	-	-	-	-	-	-	-	1.75	-
Crospovidone(mg)	-	-	-	-	-	-	-	-	-	1.75
Magnesium stearate (mg)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Talc (mg)	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Total Weight of the core tab. (mg)	35	35	35	35	35	35	35	35	35	35

Different combinations used in different ratios, including combinations of ethyl cellulose and hydroxyl propyl methyl cellulose (HPMC k4m, and HPMC k15). In addition, combinations between hydroxyl propyl methyl cellulose (HPMC k4m, and HPMC k15) and eudraget L100, eudragit RL, eudragit S100. And finally combination between hydroxyl propyl methyl cellulose (HPMC k4m, and HPMC k15) and spray dried lactose as shown in table 2.

Table 2: Composition of Coating Layer

Ingredients (mg)	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	C 10
Ethyl cellulose	60	48	-	-	-	-	-	-	-	-
HPMC K4M	60	-	60	48	48	-	-	36	30	42
HPMC K15M	-	72	60	-	-	48	60	-	-	-
Eudragit S100	-	-	-	-	-	-	60	-	-	-
Eudragit RL	-	-	-	-	72	-	-	-	-	-
Eudragit L100	-	-	-	72	-	72	-	84	90	-
Lactose	-	-	-	-	-	-	-	-	-	78
Total weight of coat (mg)	120	120	120	120	120	120	120	120	120	120

Preparation of the Outer Layer Blends

Different outer layer blend formulas to be compressed on the coated core to give final tablet were prepared, containing 5 mg of levocetrizine dihydrochloride with different amounts of cross carmellose (as super disintegrant) 2,4,6,8 and 10 mg, and Avicel pH 102 (as diluent) with 1% talc and 2% Mg stearate.

Post-Compression Parameters Evaluation

The prepared tablets (core, press coated core, and final tablet) were evaluated applying the following tests: [7, 8]
-Thickness test done by vernier instrument (Copley, UK).
-Hardness test done bytablet hardness tester (Guoming, India).
-Friability test done by friabilator (Vanguard, USA)
-Weight variation test.[9]

In-Vitro Dissolution Test[10]

In-vitro dissolution of the prepared tablets was performed using USP apparatus type II (paddle) at 37 ± 0.5°C in 900 ml dissolution medium (HCl solution pH1.2 and phosphate buffer PH6.8) at 50 rpm. Then, the withdrawn samples were filtered and analysed spectro photometriacally at their λ_{max}. Each test was done in triplicate.

Variables Effecting Release of Montelukast Sodium from the Core Tablet

Effect of Super Disintegrants Type

Three different types of super disintegrants cross carmellose, cross povidone and sodium starch glycolate) at 5% concentrations were used in (F7, F9and F10) to study the effect of super disintegrant types on the drug

release properties form montelukast sodium core tablet.

Effect of Concentration of Cross carmellose

Different percentages of cross carmellose (super disintegrant) was used in the formulation of core tablet formula (F4, F8, F9 and F10) containing 2.5, 4.5, 5 and 10%respectively to study the effect of using different crosscarmellose concentrations on montelukast sodium release from the core tablet.

Variables Effecting the Release of Montelukast Sodium from the Press Coated Core Tablet.

Effect of Different Types of Polymers and their Combination

Ten formulas (table2) of coated core tablet were prepared using different polymers (alone or in combination) in different ratios to study their effect on montelukast sodium release from press coated core tablet.

Effect of Concentration of Croscarmellose on the Release of LevocetrizineDihydrochloride form Outer Layer of Final Tablet

Different percentages of croscarmellose was used in the formulation of outer layer tablet range from 1% to 5% to in formulas 1 to 5 to study its effect on the release levocetrizine from the outerlayer.

Statistical Analysis

All data were presented as mean ± SD. Statistical analysis was performed by applying Graph Pad Prism Version 7 by choosing one-way ANOVA, followed by Tukeys test (pairwise comparisons) at 95% significance ($p<0.05$).

RESULT AND DISCUSSION

Post-Compression Parameters for the Prepared Tablets

For core tablet; the result of their post-compression parameters is shown in table 3. Friability, thickness and hardness tests for all the prepared core tablet formulas agree with the requirements of British pharmacopeia.[11]The weight variation of all prepared core tablet lies within the acceptable rang according to USP**.**

For press coated core tablet; the post-compression parameters are shown in table4. All the results for all formulas agree with the requirements of B.P. and USP.

The weight of (C1-C10) formulas coating layer equal 120 mg and compressed using punch with 8 mm die diameter. The hardness of the press coated core tablets slightly increased as the ethyl cellulose concentration was increased (C1-C2) due to high compressibility of ethyl cellulose.[12]the weight of the tablets formulas C1-C10 composes of 35 mg (weight of core tablet) + 120 mg (weight of coating layer) so the total weight is 155 mg.

Table 3: Post-Compression Parameters of Core Tablet Formulas

Formula	Thickness (mm)	Hardness (kg/ cm^2)	Friability%	Weight variation (mg)
F 1	4.11±0.01	4.75±0.03	0.71±0.02	35±0.05
F 2	4.12±0.02	4.82±0.05	0.61±0.02	34±0.03
F 3	4.05±0.01	4.72±0.03	0.58±0.03	36±0.01
F 4	4.15±0.03	4.87±0.04	0.60±0.03	35±0.04
F 5	4.06±0.05	5.02±0.02	0.46±0.06	33±0.02
F 6	4.11±0.05	4.77±0.05	0.39±0.01	36±0.03
F 7	4.02±0.04	4.43±0.03	0.53±0.02	35±0.03
F 8	4.10±0.02	4.18±0.02	0.67±0.05	35±0.01
F 9	4.02±0.03	4.20±0.04	0.50±0.03	35±0.02
F10	4.13±0.04	4.10±0.05	0.63±0.02	34±0.04

The weight of all the prepared tablet lies within the range of USP weight requirements.

The outer layer of the final tablet contains levocetrizinedihydrochloride as active ingredient. For

the final tablet; the results of post-compression parameters are gained as follow: for thickness was (11.09-11.15 with SD±0.04), hardness was (4.72-4.87 with SD±0.03) friabilityagree with the requirements of British pharmacopeia andthe weight of all the prepared tablet lies within the range of USP weight requirement.

Weight of the final tablets calculated by summation of core tablet weight plus the weight of polymers used in coating process, and the weight of outer layer so the weight of final tablet composed of 35 mg (core tablet weight) + 120 mg (coating layer weight) +200 mg (outer layer weight) =355 mg as final weight of tablet as shown in table 6.

In-Vitro Dissolution Test

Variables Effecting Release of Montelukast Sodium from the Core Tablet

Effect of Super Disintegrant Types

Formula F7 (contains cross carmellose), F9 (contains sodium starch glycolate) and F10 (contains cross povidone) were formulated using 5% of different types of superdisintegrants. Figure 1 showed that F7 have faster dissolution rate where 100% release of montelukast sodium from the core tablet obtained within 5 minutes this significant difference ($p\leq0.05$) may be due to the rapid swelling of crosscarmellose leading to rapid disintegration of core tablet into very small particles .[13]While F9 and F10 showed slow dissolution rate since sodium starch glycolate in F9 tend to form viscous gel around the disintegrated particles leading to

slow down the release,[14] and the presence of crosspovidone in F10 tend the tablet disintegrate into large particles leading to aggregation of particles causing slow release of drug.[15, 16]

Effect of Concentration of Crosscarmellose

Figure2 shows that as the concentration of crosscarmellose increased (F3, 6, 7 and 8) the dissolution rate is increased since higher concentration of crosscarmellose lead to speed up tablet break down leading to increase surface area resulting in higher dissolution rate.[17]

Table 4: Post -Compression Parameters for Press Coated Tablet

Formula	Thickness (mm)	Hardness (kg/cm^2)	Friability%	Weight variation
C 1	8±0.02	11.25±0.06	0.41±0.05	153±0.02
C 2	8±0.03	10±0.04	0.43±0.02	157±0.01
C 3	8±0.03	10.75±0.03	0.32±0.06	154±0.05
C 4	8±0.04	9.75±0.04	0.72±0.03	156±0.04
C 5	8±0.03	9.75±0.08	0.68±0.03	153±0.04
C 6	8±0.01	9.75±0.08	0.5±0.04	156±0.02
C 7	8±0.04	9.25±0.08	0.44±0.01	155±0.03
C 8	8±0.03	10.5±0.03	0.43±0.05	157±0.01
C 9	8±0.04	9.75±0.03	0.67±0.02	153±0.04
C 10	8±0.02	9.75±0.08	0.52±0.04	156±0.02

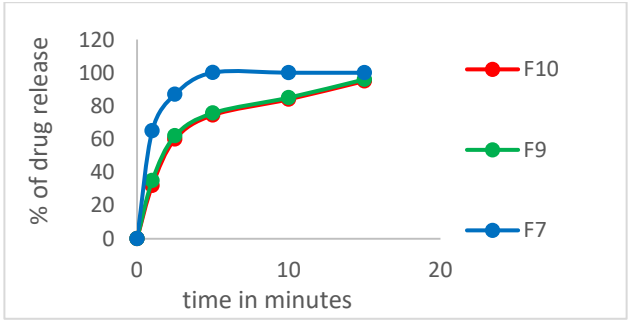

Figure 1: Release of Montelukast Sodium from Core Tablet Containing 5% of Crosscarmellose (F7), Sodium Starch Glycolate (F9) And Crosspovidone (F10) In Phosphate Buffer pH 6.8.

There is no difference noticed in dissolution rate when using 5% crosscarmellose (F7) in comparison to 10% crosscarmellose (F8) indicating limited concentration for super disintegrant is required to get its optimum effectiveness so no need to use higher concentration. Therefore; F7 is chosen for next work.

Effect of Different Types of Polymers and Combination of Polymers on the Release of Montelukast Sodium from the Press Coated Core Tablet.

Several coating formulas (C1-C10) for the core tablet were prepared in order to get the best coating that achieve the predetermined lag time release for montelukast sodium (6 hours) by using different types of polymers and polymers combination (compressed using 8 mm diameter die punch size and 120 mg coat weight) as shown in table 2.

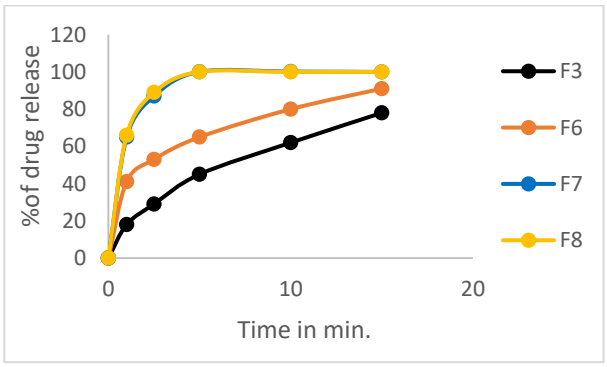

Figure 2: Release of Montelukast Sodium from Core Tablet Containing Different Concentrations of Crosscarmellose: 2.5% (F3), 4% (F6), 5 %(F7) and 10% (F10) In Phosphate Buffer (pH 6.8).

Formulas C1-C3 where ethyl cellulose(EC), hydroxyl propyl methyl cellulose (HPMC k4m, and HPMC k15) are used as coating layer in combination with different ratios that gave lag time for montelukast sodium release exceeded 7 hrs this can be attributed either to the hydrophobic nature of EC that impair the penetration of dissolution media to the core tablet or the hydrophilic nature of HPMC that will form a viscous gel network around the core tablet leading in both cases to prolong the lag time required to release of montelukast sodium.[18, 19]

Formulas C4-C9 where eudragit polymers (Eu S100 and Eu L100) which are pH dependant polymer (decompose in pH 6-7) and Eu RL (which is time dependant) were added to HPMC k4m, and HPMC k15 which are time dependant in order to remodelling characteristics of HPMC. Formula C4-C6 containing EuL100- EuRL used gave release with 6.75 – 7.25 hours while C7 containing Eu S100 showed release within first 2 hours, this could be attributed to incompatibility between Eu S100 with HPMC k15. With changing the ratios of the pH dependant polymers eudragit L 100 (which Decomposes in pH rang 6-7) to hydroxyl propyl methyl cellulose (HPMC k4m) in formulas C8 and C9 (70:30 (84mg: 36 mg) and 75:25 (90mg: 30mg)) showed release of the drug within6hrs and 5.5 hrs respectively, so formula C8 gave the target lag time required to match the maximum concentration of drug at predetermined time.Formulas C10 where spray dried lactose used in combination with HPMC k4m in ratio of 35:65 (42 mg: 78 mg) gave release of montelukast sodium after exactly 6 hours. Therefore, C8 and C10 were selected to give the required lag time for montelukast sodium release.

Effect of Concentration of Crosscarmellose on the Release of Levocetrizine Dihydrochloride form Outer Layer of Final Tablet.

Five formulas (T1-T5) containing levocetrizine dihydrochloride as active ingredient formulated with different percentages of crosscarmellose as super disintegrant to study its effect on levocetrizine dihydrochloride release from outer layer of final tablet. The results showed that T5 (5%crosscarmellose) had faster drug release where 100% release obtained within only 5 minutes and it is significantly different from other formulas T1-T4 which required about 20 minutes to give their maximum release($p \leq 0.05$) and that was due to the higher concentration of super disintegrant in T5 that speed up the breakdown of tablet leading to increasing surface area resulting in higher dissolution rate.Figure3 shows release profile of levocetrizine dihydrochloride from outer layer of final tablet.

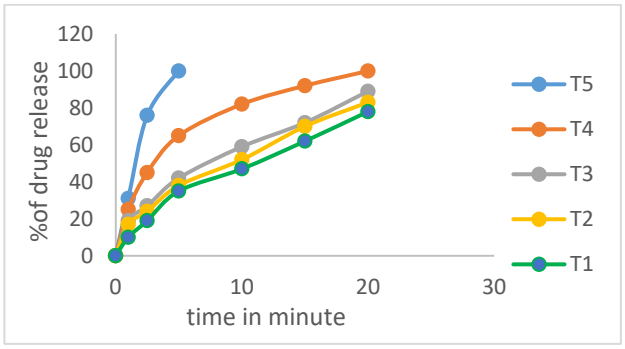

Figure 3: Release Profile of Levocetrizine Dihydrochloride from Outer Layer of final tablet in 0.1N HCl pH 1.2.

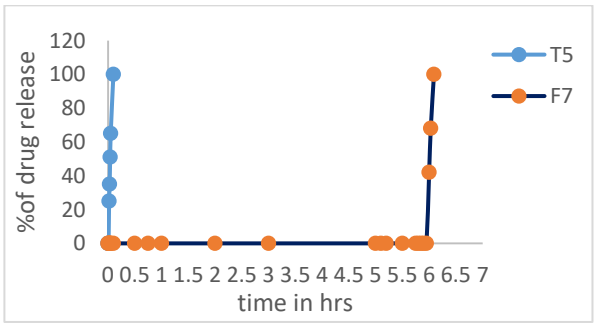

Figure 4: Release of Levocetrizine Dihydrochloride and Montelukast Sodium from Selected Final Tablet in 0.1 N HCl (pH 1.2) and Phosphate Buffer (pH 6.8).

From the dissolution test, the final tablet (composed of core tab F7 + coating layer C8 or C10 + outer layer T5 and compressed with 11 mm die diameter and total tablet weight 375 mg) gave 2 pulse release profile where the first pulse (release of levocetrizine dihydrochloride) in first 5 minutes and second pulse (release of montelukast sodium) after 6 hrs lag time this may provide maximum plasma concentrations of the two drugs at time of its maximum need. Figure 4 show the release of levocetrizine dihydrochloride and montelukast sodium from selected final tablet.

CONCLUSION

Double pulse press coated tablet can be prepared containing montelukast sodium and levocetrizine dihydrochloride separated by a coating layer to prevent their incompatibilities and can be given at 10 p.m., to get quick relieve of asthmatic symptoms upon first pulse release of levocetrizine dihydrochloride also can prevent nocturnal asthma attack at sleeping time (in early morning) upon second pulse release of montelukast sodium after 6 hrs lag time.

Acknowledgments: The authors would like to thank Al-Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad-Iraq for its support in the present work.

REFERENCES

1. Bandgar A. A., Joshi D. G., Kurade D. S. Pulsatile drug delivery with press coated techniques, International journal of pharma research & review, 4(11), 2015:55-75.
2. Brahma G.K., Gali G.V. Chrono therapeutics drug delivery systems challenges to pharmaceutical field. Journal of global trends in pharmaceutical sciences, 3(3), 2012; 778-791.
3. Singh R.,Sharma P.K., Malviya R. Review on chronotherapeutics - a new remedy in the treatment of various diseases. European journal of biological sciences2 (3), 2010; 67-76.
4. Sajan J., Cinu.T.A. , Chacko A.J., Litty J., Jaseeda T. Chrono therapeutics and chrono therapeutic drug delivery systems. Tropical Journal of Pharmaceutical Research, 8 (5), 2009: 467-475.
5. AlnoorMalick M.D., J. Grant J. A. Antihistamines in the treatment of asthma. Allergy, 52(34), 1997: 55-66.
6. Gupta M. M., Niraj Gupta, Bhupendra S. Chauhan and ShwetaPandey.Fast disintegrating combination tablet of taste masked levocetrizinedihydrochloride and montelukast sodium: formulation design, development, and characterization. Journal of Pharmaceutics.2014, (2014) Article ID 568320, 15 pages.
7. Ali K. Abbas Al-Obaidy, Nidhal KhazaalMaraie. Optimization and evaluation of time programmed press coated tablets for atenolol. World Journal of Pharmaceutical Sciences, 1(4), 2013: 130-137.
8. Iman S. Jaffar, Nidhal K. Maraie. Formulation and in vitro evaluation of buccalmucoadhesive tablets of promethazine HCl, International Journal of Pharmaceutical Sciences Review and Research. 24(1), 2014, 61-69.
9. Nidhal K. Marie.New drug delivery system of diclofenacsodium for its application in therapeutic embolization strategy. Al Mustansiriyah Journal of Pharmaceutical Sciences (AJPS).Vol. 4, No.1, 2007.
10. Certificate of Analysis. Quality control testing and research application. BIOTREND Chemicals AG. 2016.
11. Sivakranth. M, Abdul S.Althaf ,Rajasekhar.S. Formulation and evaluation of oral fast dissolving tablets of sildenafil citrate. International Journal of Pharmacy and Pharmaceutical Sciences. 3(2), 2011, 112-121.

12. Scott Vass, Hua Deng and Ali R. Rajabi-Siahboomi. Investigation of Ethylcellulose in the Preparation ofTheophylline Extended Release Inert Matrix Tablets.American Association of Pharmaceutical Scientists (AAPS) Annual Meeting.2008.

13. Mallikarjuna settee, V.R.M gupta. Development of fast dispersible aceclofenac tablet: functionality of super disintegrant. Indian journal of pharmaceutical science. 70 (2), 2008, 180–185.

14. Preeti P. Sikchi, Prof. Dr. P. V. Kasture. Comparative study of formulation and evaluation of controlled release drug with different polymeric substances. Shivaji University [thesis]. 2015.

15. Vinod Kumar M. Formulation and evaluation of meclizine HCl orally dispersible tablets by using natural super disintegrants. International Journal of Pharma Sciences and Scientific Research. 2 (1), 2016, 53-80.

16. Mohana chandran P.S., Sindhumol P.G, Kiran T.S. Superdisintegrants: an overview. International Journal of Pharmaceutical Sciences Review and Research. 6(1), 2011:105-109.

17. Alkazzaz SZ, Ali WK. Design and In-Vitro Evaluation of Colon Targeted Prednisolone Solid Dispersion Tablets.Uk journal of pharmaceutical and biosciences. 3(6), 2015, 30-41.

18. Pasqualoto KF, Funck JA, Silva FE, Kratz C. Development and evaluation of amoxicillin formulations by direct compression: influence of the adjuvants on physicomechanical and biopharmaceutical properties of the tablets. *Acta* Farmacéutica *Bonaerense*, 24(1), 2005, 39-47.

19. Dineshmohan S, Gupta VR, Ramesh A, Harika V, Sravani T. Effect of HPMC and ethyl cellulose polymeric granules and its combinations in press coated tablets of lornoxicam: fabrication and in vitro characterization. International Current Pharmaceutical Journal. 4(10), 2015: 447-452.

Source of Support: Nil, **Conflict of Interest:** None.