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# Treating Symptoms of Morning Sickness: The First Dual Release Combination of Doxylamine-Pyridoxine

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**ABSTRACT**

Modified release tablet preparations are sought when there is a need to provide clinical solutions which are not achieved optimally with the standard release products. Nausea and vomiting of pregnancy (NVP) affect most pregnancies. Symptomatic treatment aims to improve woman's quality of life, and counteract dehydration, electrolyte imbalance, need for hospitalization and attendant risk of maternal and fetal complications. Until recently, the only agent approved by Canada, USA, South Korea. Israel and Singapore has been the delayed release combination of doxylamine and pyridoxine (Diclectin®/ Diclegis®).

All other countries worldwide do not presently have a pregnancy- approved anti emetic drug. Due to its delayed release properties, Diclectin®/ Diclegis® begins to exert its antiemetic effect 6-8 hours after ingestion, and hence symptom relief may be delayed and necessitate the use of an immediate release medication. In November 2016 the FDA approved Bonjesta®, a novel, dual- release combination of doxylamine and pyridoxine, whereby a rapid release phase is followed by a delayed release phase, thus overcoming the time delay in action of the delayed release combination of doxylamine and pyridoxine. In this article we review the unique properties of this new drug in the context of other medications where modified- release forms have been effective.

**Keywords:** Nausea and vomiting of pregnancy, Doxylamine, Pyridoxine, Pyridoxal 5 phosphate, Dual released doxylamine-pyridoxine, Delayed release doxylamine- pyridoxine.

## INTRODUTION

### Clinical aspects of NVP

Nausea and vomiting of pregnancy, affecting up to 80% of women during gestation is of unknown etiology [1-4]. Hormonal increase during the first trimester of pregnancy, especially human chorionic gonadotropin (hCG), estrogen and progesterone, have been implicated. An association between Helicobacter pylori infection and severe NVP has been documented [5-7] and genetic susceptibility for NVP includes familial recurrence, monozygotic twin pair correlation, and previous history of HG [2,8,9].

Symptoms of NVP typically start between 4 and 9 weeks of pregnancy and subside by 12 to 16 weeks of pregnancy; however, in up to 15% of women, symptoms continue till 20 weeks of gestation, and up to 10% of women suffer throughout their entire pregnancy [2,3].

The most severe form of NVP, hyperemesis gravidarum (HG), affects between 0.3–2% of pregnancies and commonly requires hospitalization because of persistent nausea and vomiting, weight loss, dehydration, electrolyte imbalances, and nutritional

deficiencies [2-4].

Studies have shown that initiation of antiemetic drugs prior to symptoms lessen the severity of symptoms and reduce the recurrence of HG [10,11]. NVP can adversely impact women's quality of [3,12-15] characterized by frustration, helplessness, resentfulness, and depression [14,15]. In severe cases of NVP, some women choose to electively terminate their pregnancy [16,17]. The 2012 total economic burden of NVP in the USA was estimated at US$ 1,778,473,782, with a mean cost of US$ 1,827 per case [18].

**Management of NVP**

In cases of mild NVP, lifestyle and dietary modifications effectively manage the symptoms [19,20]. While several classes of antiemetic drugs have been proven effective in the treatment of nausea and vomiting caused by chemotherapy, motion sickness, GI conditions or cyclic vomiting [21], their use in pregnancy lacks data on maternal efficacy and fetal safety [22]. The only drug approved for the treatment of NVP in the USA, Canada, South Korea, Singapore and Israel is the delayed-release formulation of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, after its efficacy and fetal safety has been documented [23-30].

A potential challenge is that, the delayed release combination of doxylamine and pyridoxine exerts its antiemetic effect 6-8 hours after ingestion, and hence symptom relief may be delayed and necessitate the use of an immediate release medication. Bonjesta®, a novel, dual- release combination of doxylamine and pyridoxine, whereby a rapid release phase is followed by the delayed release phase, has been approved in the USA in November 2016.

We herein review this novel dual release combination of doxylamine and pyridoxine in the context of other recently approved drugs introduced with dual release properties. We believe that this new trend of developing dual release combinations will become much more prevalent, and hence pharmacists should be more familiar with this development.

**Clinical effectiveness of the delayed-release combination of doxylamine /pyridoxine**

Initially, this agent was formulated as a delayed-release combination of 10 mg doxylamine succinate, 10 mg pyridoxine, and 10 mg dicyclomine HCl [23,31]. However, in 1976, an eight-way study of doxylamine, pyridoxine HCl, and dicyclomine showed that dicyclomine did not confer an independent antiemetic effect, and consequently, Bendectin® was reformulated to contain only 10 mg doxylamine succinate and 10 mg pyridoxine HCl [32-34].

While the parent drug doxylamine has been shown to be antiemetic, recent evidence suggests that for pyridoxine it is its pyridoxal 5 phosphate metabolite which is the bioactive moiety [35].

The clinical effectiveness of the delayed-release combination of doxylamne and pyridoxine has been repeatedly documented in randomized, controlled trials as well as in open, controlled post-marketing studies [36-40].

The dose of the delayed-release doxylamine /pyridoxine for NVP is two tablets at bedtime, one in the morning, and one in the mid-afternoon. This delayed-release formulation permits the antiemetic action to occur 6 h after ingestion; therefore, the bedtime dose would be effective in the early morning, the morning dose would be effective around noonand the mid-afternoon dose would be effective in the evening, providing 24 h control of NVP symptoms. An apparent disadvantage is the lack of immediate effect, which was one of the reasons for the development of its dual release combination.

**The dual release combination of doxylamine-pyridoxine**

The dual release combination of doxylamine and pyridoxine was approved by the FDA in November 2016 and was introduced to the American market in April 2018 [41].

The drive for the development of an optimized reformulation of the delayed release combination of doxylamine and pyridoxine stemmed from several clinical perspectives:

1) To combine a fast acting form of doxylamine/ pyridoxine with the delayed release form, thus conferring an immediate antiemetic effect which was not available with the delayed release combination.
2) To decrease dosing from three times/day (morning, noon and evening) to twice a day, thus aiming to improve women's adherence during the challenging days of nausea and vomiting symptomatology.
3) To decrease variability in serum concentrations of the active components of the medication.

**Formulation and dose**

The dual release combination of doxylamine and is a multilayer, extended-release tablet consisting of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and an immediate-release coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, delivering a total of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. The new formulation allows for a rapid relief of NVP symptoms, and for sustained therapeutic effect, controlling nausea and vomiting symptoms that occur in the morning, throughout the day and into the night. The immediate-release portion in the coating layer allows for a fast rate of absorption and a rapid relief of NVP symptoms. Of importance, the absorption of the immediate-release portion of the dual release combination is not affected by food. The immediate-release coating along with the delayed-release enteric-coated core makes it an extended-release drug with a continuous pharmacodynamics effect.

The dose of each active ingredient in the dual release combination of doxylamine and pyridoxine tablets is double that of the delay release formulation, so the maximum daily recommended dosing is decreased from four tablets with the delayed release to two tablets per day with the dual release (i.e. one tablet in the morning and one tablet at bedtime. Hence, the formulation and schedule of administration of the dual release formula reduces the pill burden and is likely to improve patient adherence. In a secondary analysis of a clinical trial with the delayed-release combination of doxylamine succinate and pyridoxine hydrochloride it was demonstrated that the number of daily pills was negatively associated with patient adherence [42]. This is clinically important for pregnant women suffering from NVP who have difficulties in swallowing tablets and need to take frequent small meals. In addition, reduction of pill number reduces variations in the effective concentrations of doxylamine and pyridoxal 5'-phosphate.

The dosing regimen begins with one tablet taken at bedtime (Day 1). If NVP symptoms persist on Day 2, a second tablet is to be added in the morning to control NVP symptoms throughout the day. Hence, the maximum recommended dose is two tablets per day, one in the morning and one at bedtime.

**Pharmacokinetics of the dual release combination**

*Subjects and methods*

1. In a single-dose, crossover study, 24 premenopausal women under fasting conditions received one dual release tablet (20 mg doxylamine succinate and 20 mg pyridoxine).
2. In a multiple-dose, crossover clinical trial, one dual release (20 mg doxylamine succinate and 20 mg pyridoxine) tablet was given twice daily for 11 days to 52 premenopausal women.
3. In a single dose, cross over clinical trial conducted in 23 healthy premenopausal women, the effect of administration of a high fat, high calorie meal was studied.
    1. In the Single-dose study, the dual release form was bioequivalent to two combination tablets of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride based on systemic exposure (measured as the area under concentration time curve-AUC) and peak concentrations (Cmax) of doxylamine and baseline corrected pyridoxal 5′-phosphate, the active metabolite of pyridoxine. (Table 1).

**Table 1:** Dual release combination of doxylamine- pyridoxine in healthy non-pregnant women.

| | | **Dual release combination** Mean ± SD | | | | |
|---|---|---|---|---|---|---|
| | | **$AUC_{0-t}$ (ng•h/mL)** | **$AUC_{0-inf}$ (ng•h/mL)** | **$AUC_{0-72}$ (ng•h/mL)** | **$C_{max}$ (ng/mL)** | **$T_{max}$[b] (h)** |
| **Doxylamine** | **N=54** | 1468.1 ± 267.9 | 1536.8 ± 506.3 | --- | 93.4 ± 16.9 | 4.6 (3.6-6.6) |
| **Pyridoxine** | **N=50** | 44.4 ± 16.9 | 42.5 ± 14.8 | --- | 48.2 ± 28.9 | 0.8 (0.7-5.8) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Pyridoxal**[a] | **N=50*** | 407.8 ± 54.9 | 265.8 ± 63.9 | --- | 58.9 ± 17.0 | 3.0 (0.8-5.0) |
| **Pyridoxal 5′-phosphate**[a] | **N=60** | --- | --- | 1186.2 ± 672.2 | 30.1 ± 9.2 | 9.0 (3.0-16.0) |

*N=50 for $AUC_{0\text{-}inf}$

[a] Baseline corrected values

[b] Median (range)

2. In the Multiple dose study, the dual release drug was bioequivalent to one combination tablet of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride given three times daily (1 tablet in the morning, 1 tablet in the afternoon and 2 tablets at bedtime) (Table 2).

**Table 2:** Multiple-dose pharmacokinetics of the dual release combination of doxylamine- pyridoxine given twice daily to non-pregnant women in multiple dose.

| | | **Dual release combination** Mean ± SD | | | | |
|---|---|---|---|---|---|---|
| | | **$AUC_{0\text{-}27}$ (ng•h/mL)** | **$AUC_{0\text{-}14}$ (ng•h/mL)** | **$AUC_{0\text{-}8}$ (ng•h/mL)** | **$C_{max}$ (ng/mL)** | **$T_{max}$ (h)** |
| **Doxylamine** | **N=43** | 2979.5 ± 686.0 | 1473.6 ± 808.9 | 883.6 ± 228.3 | 176.6 ± 48.5 | 3.6 (21.0-40.0) |
| **Pyridoxine** | **N=43** | 80.0 ± 24.9 | 86.3 ± 17.4 | 45.2 ± 16.2 | 49.7 ± 26.9 | 0.4 (0.3-17.4) |
| **Pyridoxal**[a] | **N=43** | 1531.4 ± 300.0 | 898.1 ± 184.6 | 647.1 ± 149.7 | 185.6 ± 43.6 | 2.3 (1.0-16.0) |
| **Pyridoxal 5′-phosphate**[a] | **N=43** | 1752.7 ± 557.8 | 833.7 ± 274.9 | 436.9 ± 146.0 | 85.2 ± 24.7 | 18.1 (2.0-68.0) |

[a] Baseline corrected values

[b] Median (range)

3. The fatty food resulted in delayed the absorption of doxylamine, pyridoxine and pyridoxine metabolites from the dual release form. This delay was associated with lower peak concentrations due to decrease in the extent of absorption. The delayed absorption with food as measured by Tmax was less severe with the dual release formulation (Table 3).

**Table 3:** In healthy premenopausal adult women Pharmacokinetics of doxylamine and pyridoxine metabolites following a single dose administration of the dual release combination under fed and fasted conditions.

| | | **Dual Release combination N=32** | | | | |
|---|---|---|---|---|---|---|
| | | **$AUC_{0\text{-}t}$ (ng•h/mL)** | **$AUC_{0\text{-}inf}$ (ng•h/mL)** | **$C_{max}$ (ng/mL)** | **$T_{max}^{b,c}$ (h)** | **$T_{1/2el}$ (h)** |
| **Doxylamine** Mean ± SD | **Fasted** | 1223.5 ± 289.1 | 1321.7 ± 315.9 | 85.0 ± 10.9 | 3.7 (2.5-5.5) | 12.9 ± 2.6 |
| | **Fed** | 1252.8 ± 264.0 | 1254.4 ± 242.0 | 66.5 ± **1**4.2 | 9.5 (5.0 – 25.0) | 12.8 ± 2.30 |
| **Pyridoxine** Mean ± SD | **Fasted** | 34.3 ± 10.7 | 35.0 ± 8.0 | 39.8 ± 19.3 | 1.8 (0.3-4.6) | 0.9 ± 0.1 |
| | **Fed** | 22.4 ± 9.3 | 24.0 ± 10.2 | 13.5 ± 2.8 | 8.3 (2.0 – 24.0) | 1.3 ± 2.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Pyridoxal**[a] Mean ± SD | **Fasted** | 204.4 ± 40.0 | 246.0 ± 33.5 | 63.0 ± 16.8 | 2.5 (0.8-5.0) | 8.0 ± 3.9 |
| | **Fed** | 204.3 ± 35.7 | 249.3± 44.0 | 33.1 ± 8.1 | 6.0 (1.0-21.0) | 12.5 ± 7.3 |
| **Pyridoxal 5′-phosphate**[a] Mean ± SD | **Fasted** | 1021.7 ± 718.5 | --- | 27.4 ± 9.7 | 4.0 (3.0-71.8) | --- |
| | **Fed** | 1064.4 ± 386.8 | --- | 30.4 ± 11.0 | 15.0 (6.0-22.0) | --- |

[a] Baseline corrected values

[b] Profile of Subject 20 was excluded

[c] Median (range)

The full details of these results can be:

Compared to the delayed release agent, the dual release formulation showed a faster onset of action ($T_{max}$). The median $T_{max}$ on Day 11 for doxylamine was 3.5 hours with dual released combination, compared to 21 hours with the delayed release form. This is due to the immediate-release

**Clinical context of the introduction of the dual release combination of doxylamine and pyridoxine**

Although other medications, such as promethazine, (metoclopramide, ondansetron, are currently used off-label for the management of NVP, none are specifically indicated for use in pregnancy. In fact, their prescribing information state that there are no adequate and well-controlled studies in pregnant women [43,44]. The dual release form is only the second formulation ever approved by the FDA form nausea and vomiting of pregnancy, and its improved pharmacokinetic profile may render it advantageous over its older brother, the delayed release form.

**The new era of modified release drug preparations**

Modified release drug preparations are sought when there is a need to provide clinical solutions which are not achieved optimally with the standard product. We discuss here some other recently- approved drugs introduced with dual release properties. The new wave of development of dual release combinations is likely to increase, and hence pharmacists would benefit from familiarizing themselves with this development.

In 2015 Mahapatra and colleagues described the development of a modified release tablets of zolpidem containing biphasic rapid/slow delivery system [45]. The clinical issue to be

found in reference [41].

The characteristics of the dual release combination of doxylamine and pyridoxine with an early peak concentrations achieved by the immediate release coat.

portion in the coating of the dual release combination that delivers the parent drugs rapidly.

The dual and delay release formulations had similar AUC and $C_{max}$, profiles at steady state, therefore the dual release can be considered as safe as the delay release preparation.

addressed in this case was difficulty in initiating sleep coupled with difficulty in maintaining sleep, with not being able to return to sleep. This pattern, which is clinically quite common, leads to daytime distress and functional impairment. Because benzodiazepines are characterized by next-day “hangover” effect, dependence and rebound insomnia, the z drugs, including zolpidem have been gaining popularity and market share. This imidazopyridine has been shown to devoid most anxiolytic, muscle relaxant and muscle relaxant properties of benzodiazepines. However, the drug has a short elimination half-life of 2-3 hours, its ability to induce sleep is not followed by ability to maintain it. That has led the authors to develop extended release tablets of zolpidem using the biphasic delivery system technology, with sodium starch glycolate acts as a disintegrant in the immediate release part, and hydroxymethyl cellulose as a release retarding agent in the extended release core. Pharmacokinetic studies met the USP guidelines for extended release tablets [45].

The concept of combining a rapid with slow release medication was also tested in the combination of acetaminophen and oxycodone. Here too, the idea was to allow rapid control of pain, while also ensure long acting effects. Xartemis XR is an extended release tablet for oral administration containing both immediate- and extended-release components. The tablet is formulated to immediately release a portion of its oxycodone and acetaminophen. The tablet swells in gastric fluid by

diffusion of water, and hence creases the power to release the remaider of the two drugs [46]. The oral bioavailability of oxycodone is 60-87%. When using this bilayer product, Cmax of oxycodone is 3-4 hours whereas that of acetaminophen is .75-1.0 hours. Steady state of both drugs is achieved within 24 h (before the third dose administered every 12 hrs) [46].

Another example, from a different therapeutic area, is the attempt to optimize the control of type 2 diabetes. Diabetic patients already receiving a combination of pioglitazone and glimepiride, but who do not achieve adequate control of the glucose levels, are offered a bilayer preparation, whereby one side contains pioglitazone and the other glimepiride, both as immediate release drug (Duetact) [47].

It is beyond the scope of this review paper to describe recent advances in the development of drug delivery systems to overcome limited solubility, poor bio distribution and lack of selectivity. A wide range of materials, including liposomes, microspheres, polymers and carbon nanotubes are being tested for that end [48-51].

## CONCLUSION

The combination of immediate release with a delayed action is unique to the dual release combination of doxylamine and pyridoxine as it allows for the bedtime dose to be effective immediately and also provide with sustained control of NVP symptoms throughout the day.

The dual release combination provides a faster onset of action, reduced pill burden, potential improvement in patient adherence, less variation in effective serum concentrations, and shorter delay in absorption if taken with food.

## REFERENCES

1. R. Lacroix, E. Eason, R. Melzack., *Am. J. Obstet. Gynecol.* **2000**, 182(4), 931-937.
2. S. M. Clark, M. M. Costantine, G. D. Hankins., *Obstet. Gynecol. Int.* **2012**, 252676(10), 24.
3. APGO. Boston: Jespersen & Associates, LLC, **2013**.
4. T. M. Goodwin., *Obstet. Gynecol. Clin. North. Am.* **2008**, 35(3), 401-417.
5. D. Golberg, A. Szilagyi, L. Graves., *Obstet. Gynecol.* **2007**, 110(3), 695-703.
6. I. Sandven, M. Abdelnoor, B. I. Nesheim., *Acta. Obstet. Gynecol. Scand.* **2009**, 88(11), 1190-200.
7. A. V. Vikanes, N. C. Stoer, N. Gunnes., *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2013**, 167(1), 41-46.
8. M. S. Fejzo, K. W. Macgibbon, R. Romero., *J. Midwifery. Womens. Health.* **2011**, 56(2), 132-136.
9. M. S. Fejzo, S. A. Ingles, M. Wilson., *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2008**, 141(1), 13-7.
10. G. Koren, C. Maltepe., *J. Obstet. Gynaecol.* **2004**, 24(5), 530-533.
11. C. Maltepe, G. Koren., *Obstet. Gynecol. Int.* **2013**, doi: 10.1155/2013/809787.
12. C. L. Attard, M. A. Kohli, S. Coleman., *Am. J. Obstet. Gynecol.* **2002**, 186(5 Suppl), 220-227.
13. A. Lacasse, E. Rey, E. Ferreira., *B. J. O. G.* **2008**, 115(12), 1484-93.
14. P. Nguyen, A. Einarson., Women's health (London, England). **2006**, 2(5), 753-60.
15. F. Miller., *Am. J. Obstet. Gynecol.* **2002**, 186(5 Suppl Understanding), 182-183.
16. P. Mazzotta, D. E. Stewart, G. Koren., *J. Psychosom. Obstet. Gynaecol.* **2001**, 22(1), 7-12.
17. C. Piwko, W. J. Ungar, T. Einarson., *Curr. Med. Res. Opin.* **2007**, 23(4), 833-40.
18. C. Piwko, G. Koren, V. Babashov., *J. Popul. Ther. Clin. Pharmacol.* **2013**, 20(2), 10.
19. A. Einarson, C. Maltepe, R. Boskovic., *Can. Fam. Physician.* **2007**, 53(12), 2109-2111.
20. D. Jewell, G. Young., *Cochrane. Database. Syst. Rev.* **2003**, 4, CD000145.
21. K. Scorza, A. Williams, J. Phillips., *Am. Fam. Physician.* **2007**, 76(1), 76-84.
22. S. K. Gill, A. Einarson., *Expert. Opin. Drug. Saf.* **2007**, 6(6), 685-694.
23. R. L. Brent., *Reprod. Toxicol.* **1995**, 9(4), 337-349.
24. T. R. Einarson, J. S. Leeder, G. Koren., *Drug. Intell. Clin. Pharm.* **1988**, 22(10), 813-824.
25. P. M. McKeigue, S. H. Lamm, S. Linn., *Teratology.* **1994**, 50(1), 27-37.

26. L. A. Magee, P. Mazzotta, G. Koren., *Am. J. Obstet. Gynecol.* **2002**, 186(5 Suppl Understanding), 256-261.

27. G. Koren, S. Clark, G. D. Hankins., *Am. J. Obstet. Gynecol.* **2010**, 203(6), 16.

28. ACOG., *Obstet, Gynecol.* **2018**, 131(1), e15-e30.

29. SOGC., The management of nausea and vomiting of pregnancy. *J. Obstet. Gynaecol. Can.* **2016**, 38(12), 1127-1137.

30. Motherto Baby. Nausea and vomiting. In: Maternal medical conditions fact sheets.

31. http://www.bendectin.com. Accessed: September 01, **2018**.

32. R. Brent., *Birth. Defects. Res. A. Clin. Mol. Teratol.* **2003**, 67(2), 79-87.

33. J. S. Kutcher, A. Engle, J. Firth., *Birth. Defects. Res. A. Clin. Mol. Teratol.* **2003**, 67(2), 88-97.

34. Bendectin Peer Review Report **1975**. FDA1975 Contract No.: DESI 10598.

35. I. Matok, S. Clark, S. Caritis., *J. Clin. Pharmacol.* **2015**, 54, 1429-33.

36. C. J. Geiger, D. M. Fahrenbach, F. J. Healey., *Obstet. Gynecol.* **1959**, 14, 688-690.

37. B. W. McGuinness, D. T. Binns. *J. R. Coll. Gen. Pract.* **1971**, 21(109), 500-503.

38. D. Wheatley., *Br. J. Obstet. Gynaecol.* **1977**, 84(6), 444-447.

39. R. Bishai, P. Mazzotta, G. Atanackovic., *Can. J. Clin. Pharmacol.* **2000**, 7(3), 138-143.

40. C. I. Neutel, H. L. Johansen., *Can. J. Public. Health.* **1995**, 86(1), 66-70.

41. Center for Drug Evaluation and Research: NDA 209661, Summary Review. November 7, **2016**.

42. M. M. Costantine, I. Matok, G. Chiossi., *Ther. Drug. Monit.* **2012**, 34, 569-573.

43. GlaxoSmithKline. Zofran Full Prescribing Information. Research Triangle Park, NC, United States. October **2016**.

44. Sandoz Inc. Promethazine Hydrochloride Full Prescribing Information. Princeton, NJ, United States. April **2014**.

45. A. K. Mahapatra, N. H. Sameeraja and P. N. Murthy., *A. A. P. S. Pharm. Sci. Tech.* **2015**, 16, 579-588.

46. Xartemis XR oral User Reviews & Ratings.

47. Duetact- common side effects. https://www.rxlist.com/duetact-drug.htm

48. I. A. Mohammed, B. Y. Gajera., Doi: DOI: https://doi.org/10.24941/ijcr. 31364.07.2018

49. S. Z. U. Quasim, A. Naveed, M. M. Athar., Eds.: Phoenix, DA; Ahmed, W, 32-67

50. S. Z. U. Quasim, M. I. Ali, S Irfan., *Res. J. Pharm. Technol.* **2016**, 6(2), III.

51. B. Y. Gajera, R. P. Dugar, R. H. Dave., *Br. J. Pharm. Res.* **2016**, 1, 13(6), 1-9.