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EDITORIAL

ACCELERATED STABILITY STUDY AND MICROBIOLOGICAL TESTS ON NEW ORAL MATRIX DELIVERY SYSTEMS FOR DICLOFENAC SODIUM

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ABSTRACT
An accelerated stability study was performed on diclofenac sodium controlled release matrix tablets (MT20,MT33,MT34,MT33p,MT34p) containing natural gums, semi-synthetic gum , Eudragit L100,and hydroxypropylmethylcellulose (HPMC).Drug content was found to be in the range of 90-105% in all the five matrix formulas. Applying out of stability trend rules (OOT), the best formula was found to be MT33 which contained Guar gum 15%, and gum Arabic15%. No changes in physical appearance, or organoleptic properties were observed. Microbiological tests for the five matrix tablets were evaluated [(1)]. No growth (bacteria or fungi) was detected, in preserved or non-preserved formulas despite of the gum content in these controlled release tablets.

Key words: Drug content, accelerated, Stability, new oral matrix, delivery systems, out of trend, diclofenac sodium

INTRODUCTION

The USP/NF requires expiration dates for all monograph drugs since January 1976 [(2)]. The label should bear the expiration date limiting the period during which the oral tablet retains its full label potency if stored as directed. A set of storage temperatures was provided by the USP/NF to cover the various conditions of storage. These ranged from the freezing of 10°C, refrigerator between 2-8°C, cool place between 8-15°C, controlled temperature between 15-30°C, room temperature, up to 40°C with protection from light and moisture.

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Accelerated stability based on chemical kinetics was demonstrated by Garret and Carper since 1955 [3] .The WHO stated the temperature and relative humidity for the accelerated stability conditions in climatic zone 1V as 40 ± 2C /75% ±5 RH for six months [4] .

In 1971 the Food and Drug Administration (FDA) published a set of guide lines: Manufacturing and controls for investigational new drug application (IND) and new drug application (NDA) which defined in greater details the stability information required for new drug application [2]. The tablet physical parameters in (IND) phase 111 are surface appearance, friability, fragility, hardness, disintegration, color, weight variation, odor, and moisture and dissolution rate. Nowadays many guidelines are used for stability. They include ICH (International conference for Harmonization), CPMP (Committee for proprietary medicinal products) FDA (Food and drug Administration) and WHO [5-8].

The purpose of stability study is to ensure the efficacy, safety and quality of drug, and shelf life determination. In 1987 the FDA published the guidelines for submitting documentation for stability of human drugs and biologics [2]. They include tests for appearance, friability, hardness, color, odor, moisture, strength, and dissolution. The stability should include at least three batches in a marketing container used for study under the specified storage conditions [9]. The factors affecting stability are storage time, storage conditions, type of dosage form and container and closure systems. Stress conditions in accelerated stability studies [10] at several temperatures, applying Arrhenius equation, were used for estimation of shelf life of drugs.

The Arrhenius Approach which is applied for drugs with determined rate of reaction has several drawbacks. The most serious of these drawbacks are, linear regression is applied even though the data are not linear [11] .

In the Sudan, where there are different climatic conditions from the Sahara to the sub-tropical conditions which made the stability of pharmaceuticals of crucial importance, especially with regard to new drug delivery systems.

The objectives of the present study were to evaluate the drug content in accelerated stability of new matrix formulations, of diclofenac sodium, 100mg, which was proved to be controlled release matrix delivery systems [12]. The microbiological burden was assessd in gum matrix tablets, comparing preserved tablets with non-preserved ones.

In a previous study three controlled release matrix tablets from Eudragit L100 (methacrylic cid-methylmethacrylate copolymer) 6% plus hydroxypropylmethylcellulose (HPMC) 20% (MT20), Guar gum15 % plus Gum Arabic 15% (MT33), and Xanthan gum 15% plus gum Arabic 5% (MT34) were proved to be new oral drug delivery systems [12] . The formulas, MT33, MT34 were preserved with both 0.18 % methylparaben and 0.02% propylparaben to give MT33p and MT34p respectively [13] .

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The gums incorporated, especially acacia, were reported to be susceptible to microbiological contamination [14] .Being susceptible to such deterioration, we preserved these gum- containing formulas (MT33, MT34). The compendia method (BP) stated a limited bioburden in oral tablets with absence of the pathogenic bacteria as E. coli, S. typhi, and S. aureus [15] .

MATERIALS AND METHODS

Chemicals and reagents:

All solvents were HPLC grade, while the other chemicals were of analytical

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grade. The standard diclofenac sodium was obtained from Horst von Valtier, Hamburg, and Germany.

All solvents and reagents were purchased by Wafrapharma Laboratories Sudan.
The internal standard was propylparaben from G. Amphray Laboratories India. Nutrient agar and Saubourauds dextrose agar were obtained from Oxoid LTD, Basingstroke, Hampshire and England.

Instrumentation:
The stability studies were conducted on five matrix tablets (MT20, MT33, MT34, MT33p, MT34p) containing 100mg Diclofenac sodium, prepared by direct compression method. Analytical equipment used was high performance liquid chromatography (HPLC) system consisting of Knauer K1001 isocratic pump and K-2501 ultra-violet visible spectrophotometer Knauer Germany set at 272nm with a rheodyne injection valve of 20ml fixed filling loop.

The analytical column was C18, Eurosphere-100 (5mm) 4mm I.D. x 100mm. The system was coupled with pre-column, degasser, Knauer, and Eurochrome 2000 software for HPLC analysis.

Analysis was made with reference to physical appearance and content after storage in stability chamber, Rumed, Rubarth Apparate GmbH Germany, at 40C and 75% relative humidity for 6 months ([4]) .The study was done in darkened chamber [(16)]. The storage conditions were used for zones i, ii, iii, and 1Vfor accelerated stability study (40C and 75%RH) which were designed for solid oral dosage forms, solids for reconstitution, dry and lyophilized powders in glass vials. Samples were kept in blister packing PVC 250 m, Aluminium foil 25 m. Content analysis was performed using isocratic HPLC method, mobile phase of phosphate buffer at pH 5.5 and acetonitrile in combinations of 65 and 35V/V. Twenty (20) L were injected each time, and flow rate was one ml/minute. Microbiological tests for matrix tablets (MT20, MT33, MT34, MT33p, and MT34p) during accelerated stability study were performed using BP method [(1).]

RESULTS AND DISCUSSION

The results of determinations of diclofenac sodium content from the different matrix tablets were presented as in the histogram .Each result is a mean of three replicate measurements.

Histogram: stability data

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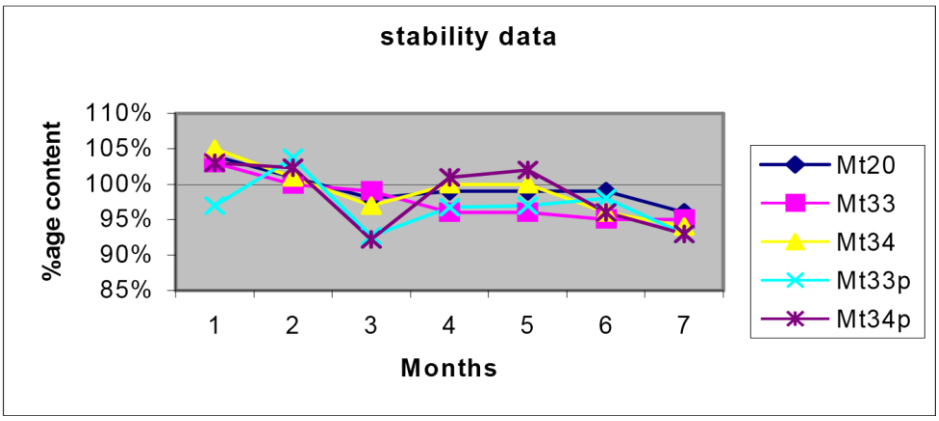

The stability profile of the five preserved and non preserved tablets were found to be between 90-105%. The two preserved formulas were out of limit at month two and six, while MT34 was within the limit for five months. The two selected candidate formulas MT20 and MT33 were within the limit for all the study time which was advocated their stability and expected reliability for use .Although the BP limit was 95% as the lower limit for stability study [17], the 90% in MT33p and MT34p of the labeled potency are recognized as the minimum acceptable level [11].

Clearly the study showed matrix tablets as passing the content requirements in solid dosage stability at the specified temperature and relative humidity (40C, and 75% RH).

Further, this agreed with the findings reported by Harpinder et al ([18]. No change in physical appearance, or organoleptic properties -color, odor and taste- was observed.

The stability study results of the diclofenac sodium matrix tablets (MT20, MT33, MT34, MT33p, and MT34p) were analyzed by the simple rule of thumb for the out of trend stability study. The rule states that the out of trend (OOT) result is a stability result that does not follow the expected trend ,either in comparison with other stability batches or with respect to previous results collected during a stability study [19] .

The sample is considered out of trend if:
Three of the consecutive results are outside some limit (eg.BP).
The result is outside ±5%of the initial result.
The result is outside ±3% of the previous result.
The result is outside ±5% of the mean of all the previous results.
Applications of the above rules for all the matrix tablets was done (tables 1-4)

Table 1: The limit of %age content in controlled release diclofenac sodium (BP 95-105%) in different matrices. Percent content w/w.

(+) complying (-) not-complying

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Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	+	+	+	+	+	+	+
MT33	+	+	+	+	+	+	+
MT34	+	+	+	+	+	+	-
MT33p	+	+	-	+	+	+	-
MT34p	+	+	-	+	+	+	-

MT= Matrix tablet, p= preserved.

Table 2: The variation of the %age content result from the limits of ±5%of the initial result. (+) within the range (-) out of the range:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104%	+	+	+	+	+	+
MT33	103%	+	+	+	+	+	+
MT34	105%	+	-	+	+	-	-
MT33p	097%	+	+	+	+	+	+
MT34p	103%	+	-	+	+	-	-

MT= Matrix tablet, p= preserved.

Table 3: The variation of the %age content result from the limits of ±3% of the previous result. (+) within the range (-) out of the range:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104%	+	+	+	+	+	+

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MT33	103%	+	+	+	+	+	+
MT34	105%	-	-	+	+	-	+
MT33p	097%	-	-	-	+	+	-
MT34p	103%	+	-	-	+	-	-

MT= Matrix tablet, p= preserved.

Table 4: The variation of the %age content result from the limits of ±5% of the mean of all the previous results. (+) within the range (-) out of the range:

Matrix	Zero time	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month
MT20	104%	101%	+	+	+	+	+
MT33	103%	100%	+	+	+	+	+
MT34	105%	101%	-	+	+	-	-
MT33p	097%	104%	-	+	+	+	+
MT34p	103%	102%	-	+	+	+	-

MT= Matrix tablet, p= preserved

From the application of the above rules of out of trend stability (tables 1-4), it was concluded that MT33 which contains Guar gum15 %and gum Arabic 15 % as controlled matrix was the best formula. The second best was MT20 which contains EudragitL100 6% and HPMC 20%. The other formulas MT34, MT33 p, and MT34 p were irregular in the stability readings which may be due to reactive or degradative effects.

No microbiological growth (bacteria or fungi) was observed after the specified incubation period for all the matrices for six consecutive months.

CONCLUSIONS

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The stability profile with regard to percent content of diclofenac sodium in the controlled release matrices (MT20, MT33, MT34, MT33p, and MT34p) was found to be between 90-105%. The two preserved matrices showed one reading out of the BP limit at the second and six month , while the formulas MT20, and MT33 were within the BP limit (95-105) for six months which advocated their stability and expected reliability for use.MT34 was out of limit at the six month. From the application of out of trend stability rules (tables 1-4), it can be concluded that MT33 which contained Guar gum 15%and gum Arabic15 % as controlled matrix was the best formula. Second best to it was MT20 which contained EudragitL100 20% and HPMC6 %. The other formulas MT34, MT33 p, and MT34 p were irregular in the stability readings which may be due to chemical or interactive effects. However, no change in physical properties was observed. No microbial growth (bacteria or fungi) was detected during the six month period of accelerated stability study in both preserved and non preserved matrices. This should exclude the necessity of preservation in these controlled release matrix delivery systems.

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REFERENCES

1. BP Appendix XV1C. Efficacy of antimicrobial preservation.1999, P1-4
2. Herbert A. L., Leon L., And Josef B. S. Pharmaceutical Dosage forms Tablets Vol 3, 1992 pages 457-496.
3. Alfred M., Physical pharmacy 4th edition. Lippincott Williams and Wilkins, 351 West Camden Street, Baltimore Maryland, USA.2001.pages 313-323.
4. WHO. Working document QAS/04.088. 2004 pages 1-11.
5. Singh Sarajit., Pharmatimes, 29, 1997, pages 29-42.
6. Singh, Sarajit, East.pharm, 60 (479) 1997, pages 41-42.
7. Singh, Sarajit, East.pharm, 61(487), 1998, pages 43-48.
8. Technical report, series, 863, WHO, Geneva, Switzerland. WHO 1996.
9. Haynes, J.D 1971. J.pharm.Sci, 60, 1971, pages 927-929.
10. Monika Bakashi, and Sarajit sigh, ICH guidance in practice, stress degradation studies on metronidazole and development of a validated stability-indicating HPLC assay method. Pharmaceutical Technology, .2003, pages 148-160.
11. Kulkarni.G.T et al. Pharmaceutics .Stability testing of pharmaceutical products: An overview. Pharmaeutics Vol 38 Nubber 04, 2004.pages 1-3.

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12. BP 2001
13. BP Appendix XV1D.Category 3. 1999 pages 1-2.
14. A.A.A. Gargar and Abdulkarim M.A. In vitro Diclofenac soium dissolution profile in new matrix delivery systems. Omdurman Journal of pharmaceutical Sciences (OJPS) No 2, 2006.pages 125-134.
15. Pharmaceutical Excipients, American Pharmaceutical association, And the Pharmaceutical Society of Great Britain. Printed in USA.
16. Kurup T.R.R Microbiological quality in pharmaceuticals. The eastern pharmacist. 1981, pages 53-69.
17. Hemant Bhagani, Mariappan T.T. and Sarajit S. Behavior of uptake of moisture by drugs and excipients under accelerated conditions of temperature and humidity in absence and presence of light.Pharmaceutical technology, 2003. Pages 44-52.
18. Harpinter Kaur et al. Uptake of moisture by drug and excipients. Pharmaceutical technology. 2003, pages 52-56
19. RhRMACMC Statistics and Stability Expert teams. Identification of outof-Trend stability results, a review of the potential regulatory issue and various approaches. RhRMACMC Statistics and Stability Expert teams.

Pharmaceutical Technology 2003 pages 38-52