Natural polymer based mucoadhesive gastroretentive tablets of Pregabalin: formulation and *in vitro*characterization

Aradhana Tiwari[1], Komal Manwani[2], Mohd. Kalim[3], Dr. Prashant Kumar Katiyar[4]
[1]Research Scholar, Kanpur Institute of Technology, Kanpur, UP, India
[2]Assistant Professor, Kanpur Institute of Technology, Kanpur, UP, India
[3]Assistant Professor, Kanpur Institute of Technology, Kanpur, UP, India
[4]Director, Kanpur Institute of Technology, Kanpur, UP, India
aradhanat849@gmail.com[1], komalmanwani17@gmail.com[2],
mohdkalim643@gmail.com[3],prashant.katiyar@kit.ac.in[4]
Corresponding Author:Aradhana Tiwari

Abstract

The aim of this investigation was to formulate gastroretentive tablets of pregabalin utilizing the potential of natural gums as mucoadhesive polymer so that the formulation could control the release of the drug thereby reducing its dosing frequency and improving the bioavailability. The angle of repose, bulk density, tapped density, Hausner's ratio and Carr's Index were found to be ranging from23.78 ± 0.5468° to 26.54 ± 0.2939°, 0.39 ± 0.0435 to 0.533 ± 0.0208 g/cm^3, 0.476 ± 0.0152 to 0.596 ± 0.0251 g/cm^3, 1.05 to 1.24 and 4.82 to 19.38 respectively. The thickness of tablets was 4.9 to 4.8 mm, hardness 4.5 kg/cm^2 and 4.1 kg/cm^2, friability 0.19% to 0.49% and the weight variation 1.8 to 1.2 %.Swelling study was performed on all the formulation for 9 h and was found to be in the range of 2.23 to 6.08. The highest degree of swelling was achieved by F7 containing a mixture of all the three gums. All the formulations were able to prolong the release of drug for more than 10 hours. Formulation F6 and F7 were able to sustain the release to higher duration with F6 and F7 releasing 87.2 and 81.6 % pregabalin respectively at the end of the 12 hours of study.

Keywords: Pregabalin, sustained release, gastroretentive, mucoadhesion, natural gum
DOI Number:10.14704/nq.2022.20.8.NQ44531 **NeuroQuantology 2022; 20(8): 5046-5053**

Introduction

Neuropathic pain is a widespread problem that affectsapproximately 7–8% of the common population and is presumed to be relatedto somatosensory system related disease or damage[1-4]. Drugs used for treating epilepsy have been used frequently used for management of neuropathic pain[5,6]. Pregabalin, chemically termed as (S)-(+)-3-aminomethyl-5-methylhexanoic acid is structurally analogousto γ-amino butyric acid(GABA) and is approved by FDA for treating neuropathic pain linked to several conditions like diabetic neuropathy and fibromyalgia[7,8]. It exhibits its action by binding to auxiliary α2δ protein subunit linked to voltage-gaurded calcium ion channels in the central and peripheral nervous systems[9].The gastric absorption of pregabalin has been known to be limited to the upper portion of the small intestine[4].The clinically marketed products of pregabalinare immediate-release (IR) formulations of 75, 150, and 300 mg strength, which need to beingested at 150–600 mg twice

per day, thus making it less complaint among the patients with chronic pain[10]. Hence controlled-release (CR) systems which develop patient compliance by reduced dosing frequency are need of the hour.

Gastro-retentive systems are capable of remaining in the gastric region for more than a few hours and hence appreciablyextend the gastric residence time of drugs[11]. Extended gastric withholdingin turn helps to provide better bioavailability, trim down drug wastage, and perk up solubility of drugs that present lower solubility in a high pH surrounding[12].

In the present study, gastroretentive system utilizing the mucoadhesive potential of naturally occurring gums has been attempted and the total duration of release was studied.

Material and Methods

Pregabalin was purchased from Yarrow Pharmaceuticals, Mumbai and all the gums, reagents and other chemicals were procured from Himedia, Qualigens and Oxford. The drug and excipients were used without purification in the state they were procured.

Preformulation[13]

The drug was subjected to evaluation of physical characters, melting point, partition coefficient, solubility and construction of calibration curve. The physical characters studied included taste, color, smell and physical features of the drug. Melting point has beenchecked using open capillary method and is uncorrected. Solubility was determined qualitatively by shaking a small unmeasured quantity of drug in 1 mL of solvent and observing for undissolved particles (if any).

***Partition Coefficient*[14]**

The partition coefficient (Log P) of pregabalin was evaluated by employing 1-octanol (10 mL) as non-aqueous phase and distilled water (10 mL)as aqueous phase using a separating funnel. Accurately weighed 5 mg of pregabalin was added to a mixture of both the phases and the phases were mixed by vigorous shaking in a separating funnel. The mixture was allowed to stand undisturbed for few hours to allow complete separation ofboth the phases. The aqueous phase was carefully withdrawn in a conical flask and analyzed spectrophotometrically after proper dilution against solvent blank.The partition coefficient was calculated using the formula as under.

$K_{o/w}$ = Concentration of drug in 1-octanol/ Concentration of drug in water

***Calibration curve of pregabalin*[15]**

A previously reported UV spectrophotometric method was used for evaluating the pregabalin content in the samples. The standard curve was constructed in the concentration range of 0.5-5.0 µg/mL.

Standard curve in distilled water

50 mg drug was solubilized in 10 mL double distilled water and quantity sufficient of distilled water was added to make up the volume up to 50 mL. The solution was diluted appropriately using the distilled water to obtain working standards of 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 µg/mL strengths. The absorbance of these working standards was spectrophotometrically determined at 210 nm and standard curve were plotted for absorbance versus concentration.

Formulation of gastroretentive tablets

The mucoadhesive gastroretentive tablets of pregabalin were formulated with various ratio and blends of the natural gums.

Pregabalin, chitosan, xanthan gum and gum moringa were accurately weighed and taken in a mortar as per the formula mentioned in Table 1. To the mix was added MCC and triturated for proper blending of the components. The powder blend was sifted using sieve no. 80. A presifted (sieve no. 80), accurately weighed quantity of magnesium stearate as well as talc were added to this blend and all the components were blended together to obtain the tablet blend. This blend was evaluated for powder characteristics and finally compressed as uncoated tablets with the help of a single punch tablet punching machine.

Table 1 Batch Formula for formulation of gastroretentive tablets

	F1	F2	F3	F4	F5	F6	F7
Pregabalin (mg)	50	50	50	50	50	50	50
Chitosan (mg)	40	-	50	-	60	-	35
Gum Moringa (mg)	70	70	60	60	50	50	40
Gum Xanthan (mg)	-	40	-	50	-	60	35
MCC (mg)	70	70	70	70	70	70	70
Magnesium Stearate (mg)	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5
Total Weight (mg)	240	240	240	240	240	240	240

Assessment of powder characteristics

Angle of repose (θ)

Angle of repose was assessed using the fixed funnel method. An accurately weighed amount of compression blend was flown down a funnel,placed at a fixed height,until the tip of heap touched the lower tip of the stem of the funnel. The averaged diameter of powder heap was calculated and the value of angle of repose was determinedby the following formula:

$$Tan\ \theta = \frac{h}{r}$$

Where, h is the distance of tip of funnel from surface; θ denotes angle of repose; and r denotesaveraged radius of the heap

Bulk and Tapped Densities

Bulk density represents the ratio of unit mass of the blend to its volume. The bulk density of the blend was calculated by placing the accurately weighed compression blend inthe density cylinder of the instrument and measuring the volume (mL). The bulk density was calculated by formula:

$$\rho b = M/Vb$$

$\rho_b$is the bulk density; M is the mass of the microspheres and V_b is the volume occupied by the blend.

For determination of tapped density the above cylinder was tapped for a 100 taps at fixed distance using tapped density apparatus. The tapped density was computed by formula:

$$\rho t = M/Vt$$

Hausner Ratio

Hausner's ratio was computedusing the values of the bulk and tapped density formula

$$\text{Hausner's Ratio} = \text{Tapped density}/\text{Bulk density}$$

Percent compressibility (Carr's Index)

Compressibility is asignificantindication that can be determined using the data of bulk and tapped density. The flowability of the blendcould beasssessedutilizing the compressibility index calculated using formula

$$I = (1 - Vf/Vo)\ X\ 100$$

Vf = tapped volume; V_0 = bulk volume

Assessment of gastroretentive tablets

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, thickness, weight variation, hardness, friability, swelling index, dissolution study.

*e*ISSN1303-5150

Hardness testing

The tablet hardness was measuredby the use of Monsanto hardness tester. Four tablets were randomly taken from each formulation and the force thatbroke the tablets was read directly form the plunger of the tester.

Friability testing

The friability testing of the tablets was done with Roche type friability tester. Twenty tablets were initially weighed ($W_{initial}$) and placed in the drumof thefriabilator. The apparatus was operated for 4 minutes (100 revolutions). The tablets were dusted and reweighed (W_{final}) and the friability percentage was calculated using formula

$$\% \text{ Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

Weight variation

Twenty tablets per formulation were collected randomly and the average weight was determined. Every single of these tablets was weighed and the deviation from average weight was computed and the weight variation percentagewas reported.

Thickness

Randomly collected tablets from each formulation subjected to measurement of thickness with the help of a digital vernier caliper.

Drug content

Twenty tablets were crushed and the amount of powder equivalent to 10 mg pregabalintaken in mL volumetric flask. The drug was dissolved in distilled water and volume was made up to the mark. 10 mL of this solution was withdrawn and dilutedup to 100 mL with distilled water. 10µg/ml solution was prepared from this solution and the absorbance at 210 nm was spectrophotometrically analyzed.

In-vitro release

Dissolution testing was performed using USP type II apparatus at paddle speed of 50 rpm. The dissolution medium consisted 900 mL of 0.1 N HCl. 5 mL of samplewaswithdrawn at prefixed time intervalsup to 12 h and the medium was replenished after each sample withdrawal. The drug concentration was calculated from absorbance at 210 nm using the calibration curve.

Swelling Index

One tablet per formulation was placed in a petridishthat contained phosphate buffer pH 7.2. After 2 h, the tablet was pulled out and kept on a tissue paper and was weighed[1]. The weighing was continued for every 2 hr, up to 9 h. The % weight gained by the tablet was computed

$$S.I = \frac{Mt - Mo}{Mo} * 100$$

S.I - swelling index; M_t = weight of tablet at the time (t); M_0 = weight of tablet at time 0.

Results and Discussion

Preformulation studies

The results obtained from the preformulation characterization of pregabalin are reported Table 2.

Table 2 Preformulation characters of pregabalin

Physical characters	White crystalline solid, metallic taste and odorless
Melting point	174-178°C
Solubility	Soluble in water, 0.1N HCl, 0.1N NaOH; slightly soluble in ethanol and methanol
Partition coefficient	1.4

Pregabalin Calibration Curve

The standard curve has been constructed in distilled water and is presented in figure 1 along with the equation for regression. The linearity was found between 0.5 to 5.0 µg/mL and the linear equation was used to determine the concentration of pregabalin in the formulations.

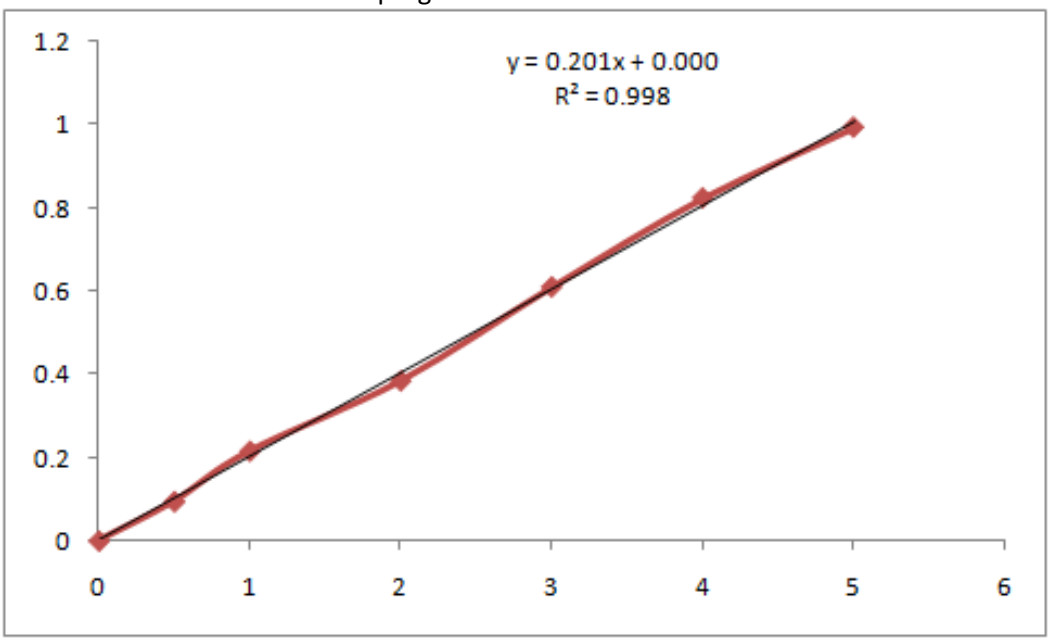

Figure 1 Standard Curve of pregabalin in distilled water

Characterization of Precompression Blends

The bulk and tapped density of the formulations ranged from 0.39 ± 0.0435 to 0.533 ± 0.0208 g/cm^3 and 0.476 ± 0.0152 to 0.596 ± 0.0251 g/cm^3 respectively. The bulk and tapped density play a vital role in pharmaceuticals as it reflects processing capabilities of the blend. It also reflects flow characters of the blend using various calculated values. The result of precompression blend characterization is presented in Table 3.

5050

Table 3 Evaluation of powder characteristics of precompression blends

Formulation code	Angle of Repose (°)	Bulk density	Tapped density	Carr's Index	Hausner's Ratio
F1	25.43	0.39	0.476	18.07	1.22
F2	25.11	0.473	0.516	8.33	1.09
F3	25.67	0.493	0.596	17.28	1.21
F4	25.22	0.416	0.516	19.38	1.24
F5	26.18	0.436	0.523	16.63	1.20
F6	25.43	0.496	0.546	9.16	1.10
F7	25.43	0.533	0.56	4.82	1.05

Angle of repose is an appraisal of the capability to powder to flow down the hopper of the tablet punching machine. The angle of repose was determined by fixed funnel technique and

was found to be ranging from 23.78 ± 0.5468° to 26.54 ± 0.2939°. The value of Hausner ratio and Carr's Index has been calculated from the data of bulk and tapped density and were obtained inbetween 1.05 to 1.24 and 4.82 to 19.38 respectively.All the results of powder characterization reveal that the precompression blends exhibited good ability to flow and get compressed in to tablets.

Assessment of gastroretentive tablets

The result of assessment of the gastroretentive tablets have been reported in Table 4.

The thickness of formulations ranged in between 4.9 to 4.8 mm. Hardness of tablet of all formulation ranged from 4.5 kg/cm^2 and 4.1 kg/cm^2. The hardness of all formulation showed the slight variation owing toingredients differences and powder properties. The friability of all formulation was in the range of 0.19% to 0.49%. All formulation exhibited lower than 1% friability and passed friability test suggesting good mechanical strength to withstand external forces while packaging and transport. The weight variation of the formulations ranged from 1.2 to 1.8 % confirming uniformity in the formulations.

Swelling study was performed on all the formulation for 9 h. All formulation was in the range of 2.23 to 6.08. The highest degree of swelling was achieved by F7 containing a mixture of all the three gums. The higher ability to swell provides higher retention in the gastrointestinal tract thus prolonging he drug release from the formulation over longer time duration.

Table 4 Tablet characteristics of gastroretentive tablets

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation (%)	Friability (%)	Swelling Index	Drug content (%)
F1	4.9	4.3	1.2	0.24	2.23	99.1
F2	4.8	4.2	2.7	0.19	2.49	97.9
F3	4.8	4.1	1.4	0.46	3.36	98.3
F4	4.8	4.3	2.8	0.41	3.68	99.2
F5	4.9	4.2	2.1	0.49	4.19	97.4
F6	4.9	4.5	2.4	0.38	5.22	98.9
F7	4.8	4.3	1.6	0.22	6.08	99.3

The dissolution study was done in 0.1M HCl medium to check the release control profile of the matrix. It was observed that of all the formulations were able to prolong the release of drug for more than 10 hours. Formulation F6 and F7 were able to sustain the release to higher duration with F6 and F7 releasing 87.2 and 81.6 % pregabalin respectively at the end of the 12 hours of study (Figure 2).

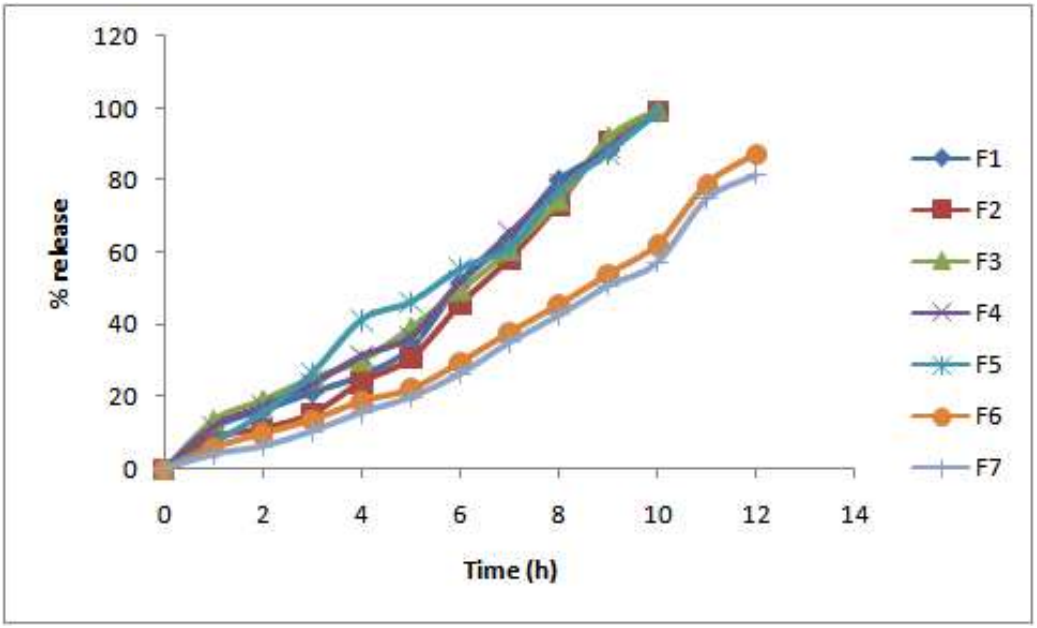

Figure 2 *In vitro* release of pregabalin from formulations

Conclusion

The results obtained from the study indicate that use of chitosan, xanthan gum and gum moringa as the mucoadhesive polymers could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments. The use of chitosan along with gum moringa was not very effective in prolonging the action and also did not produce good flow. The use of chitosan has previously been demonstrated to sustain the release of pregablin more than 8 hours when formulated as microcapsules but the drug entrapment was about 67-70 %[16,17] (Bhargav et al., 2017; Sai Vardhan et al., 2014). Xanthan gum and gum moringa was effective in higher ratio. The combination of all the three with gum moringa as the primary mucoadhesive gum was the most beneficial for gastroretention of tablets. Further *in vivo* release studies are needed to support for the conclusion of the present investigation.

Acknowledgements

The authors are thankful to RB Science, Bhopal for their guidance in completion of work and preparation of manuscript.

References

1. C. Qin, M. Wu, S. Xu, X. Wang, W. Shi, Y. Dong, L. Yang, W. He, X. Han, L. Yin, Design and optimization of gastro-floating sustained-release tablet of pregabalin: in vitro and in vivo evaluation. International Journal of Pharmaceutics (2018), doi: https://doi.org/10.1016/j.ijpharm.2018.04.011
2. Dworkin, R.H., O'Connor, A.B., Audette, J., Baron, R., Gourlay, G.K., Haanpaa, M.L., Kent, J.L., Krane, E.J., Lebel, A.A., Levy, R.M., Mackey, S.C., Mayer, J., Miaskowski, C., Raja, S.N., Rice, A.S., Schmader, K.E., Stacey, B., Stanos, S., Treede, R.D., Turk, D.C., Walco, G.A., Wells, C.D., 2010. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clinic Proceedings 85, S3-14.
3. Moulin, D., Boulanger, A., Clark, A.J., Clarke, H., Dao, T., Finley, G.A., Furlan, A., Gilron, I., Gordon, A., Morley-Forster, P.K., Sessle, B.J., Squire, P., Stinson, J., Taenzer, P., Velly, A., Ware, M.A., Weinberg, E.L., Williamson, O.D., Canadian Pain, S., 2014. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Research & Management 19, 328-335.

4. Su, T.Z., Feng, M.R., Weber, M.L., 2005. Mediation of highly concentrative uptake of pregabalin by L-type amino acid transport in Chinese hamster ovary and Caco-2 cells. The Journal of Pharmacology and Experimental Therapeutics 313, 1406-1415.
5. Yasin, H., Al-Taani, B., Salem, M.S., 2021. Preparation and characterization of ethylcellulose microspheres for sustained-release of pregabalin. Research in Pharmaceutical Sciences 16(1), 1-15.
6. Vinik A, 2005. Clinical review: use of antiepileptic drugs in the treatment of chronic painful diabetic neuropathy. Journal of Clinical Endocrinology and Metabolism 90(8), 4936-4945.
7. Ben-Menachem, E., 2004. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 45 Suppl 6, 13-18.
8. Rosenstock, J., Tuchman, M., LaMoreaux, L., Sharma, U., 2004. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 110, 628-638.
9. Fedak Romanowski, E.M., 2017. Book review: pellock's pediatric epilepsy diagnosis and therapy. J Child Neurology 32(9), 846-847.
10. S. Kim, K-M. Hwang, Y.S. Park, T-T. Nguyen, E-S. Park, Preparation and evaluation of non-effervescent gastroretentive tablets containing pregabalin for once-daily administration and dose proportional pharmacokinetics. International Journal of Pharmaceutics (2018), doi: https://doi.org/10.1016/j.ijpharm.2018.08.038
11. Kim, K.H., Lim, S.H., Shim, C.R., Park, J., Song, W.H., Kwon, M.C., Lee, J.H., Park, J.S., Choi, H-G., 2020. Development of a Novel Controlled-Release Tablet of Pregabalin: Formulation Variation and Pharmacokinetics in Dogs and Humans. Drug Design, Development and Therapy 14, 445-456.
12. Upadhyay, H.B., Pandya, S.J. & Vyas, M. 2014. A review on gastroretentive microsphere. International Journal of Universal Pharmacy and Biological Sciences, 3 (2): 429-455.
13. Ahirwar, S., Kumar, A., Sharma, R., 2021. Formulation development and in vitro evaluation of oral dispersible tablets of Olanzapine by direct compression. Journal of Pharmacology and Biomedicine 5(3), 304-311
14. Hanson KB, Hoff DJ, Lahren TJ, Mount DR, Squillace AJ, Burkhard LP. Estimating n-octanol-water partition coefficients for neutral highly hydrophobic chemicals using measured n-butanol-water partition coefficients. Chemosphere. 2019; 218: 616-623.
15. Gujral, R.S., Manirul Haque, S.K., Shanker P., 2009. Development and Validation of Pregabalin in Bulk, Pharmaceutical Formulations and in Human Urine Samples by UV Spectrophotometry. International Journal of Biomedical Science 5(2): 175-180.
16. Bhargav, A., Jeevan Mani Babu, D., Nagendra Babu, B., 2017. ormulation and evaluation of Pregabalin Microencapsules: a sustained release approach. Indian Journal of Research in Pharmacy and Biotechnology 5(1), 31-35.
17. Sai Vardhan, J., Umadevi, A.K., Lachoriya, M., Singh, J., Rajeswari, G., Kasturibai, B., 2014. Formulation and evaluation of sustained release chitosan microspheres of pregabalin for the effective treatment of epilepsy. International Journal of Current Research in Chemistry and Pharmaceutical Sciences 1(10), 120-130.

*e*ISSN1303-5150