A Comprehensive Review on NMR Spectroscopy in Detection of Brain Tumors

Bhoomi D. Patel*, Reepa M. Patel[1], Smit A. Agrawal[2], Vidhi R. Bhatt[2]

*Associate Professor, Saraswati Institute of Pharmaceutical Sciences, Dhanap, Gandhinagar, Gujarat, India – 382355.

[1]Assistant Professor, Saraswati Institute of Pharmaceutical Sciences, Dhanap, Gandhinagar, Gujarat, India – 382355.

[2]Student, Saraswati Institute of Pharmaceutical Sciences, Dhanap, Gandhinagar, Gujarat, India – 382355.

ABSTRACT:-
Perfect diagnosis should be needed for optimum management and treatment of patients with brain tumours. Proton magnetic resonance spectroscopy (1 H MRS) gives information about the brain tumor non-invasively on its biochemistry and to provide important additional information to that obtained by conventional radiology.Carrying out H1 MRS in the brain is inherently less complicated than in other tissues , in which spectra are heavily affected by magnetic field inhomogeneities, respiration artifacts, and dominating signals from the surrounding adipose tissues.The purpose of evaluate the current scenario of 1 H MRS in classifying brain tumour type and grade, for monitoring response to therapy and progression to higher grade.
KEYWORDS: 1 H MRS, Brain tumour, Diagnosis, Prognosis

I. INTRODUCTION:

Precise diagnosis is important for optimum clinical management of patients with intracranial tumours. Proton nuclear magnetic resonance spectroscopy (1 H-NMRS) is a noninvasive in vivo technique that utilizes conventional MR imaging hardware to obtain biochemical information from a individual volume of tissue after suppression of the water signal[1].Brain tumors are highly heterogeneous for histology, prognosis, and therapeutic response[2]. From proton magnetic resonance spectroscopy provides unique information about defining tumor types and grade,directing biopsy or surgical resction , planning radiation or biological therapies in accessing treatment response and understanding the mechanisms of success and failure of new treatments .The most common primary benign brain tumors arepilocytic juvenile astrocytoma and meningioma. The most common malignant brain tumors are medulloblastoma and glioblastoma. Brain tumor proton magnetic resonance spectroscopic imaging studies consistently show the reduction or absence versus control subjects of N-acetylaspartate (NAA) and total creatine, including creatine and phosphocreatine, likely due to edema and necrosis, an increase in choline-containing compounds (Cho), possibly via cell membrane disruption and altered phospholipid metabolism during rapid cell growth and neoplasia , and increased lactate, reflecting metabolically active tumor cells[3][4].The biomarkers which we obtain by using proton magnetic resonance spectroscopy (1H PMRS) provide more accurate prognosis.

DETECTION OF BRAIN TUMOR BY PROTON RESONACE SPECTROSCOPY:-

Proton magnetic resonance spectroscopy is a non invasion technique that permits in vivo measurements of certain tissue metabolites. Proton (1 H) spectroscopy is more advantageous than spectroscopy of other nuclei because 1 H has the highest sensitivity. To acquire spectra with additional software 1H NMRS can be obtained on a standard MRI scanner. Specific pulse sequences that suppress water and lipid signals[5]. The signals which are obtain by the proton mangnetic resonance spectroscopy (1H PMRS) is due to the metabolites . In the brain, the major metabolite signals that can be measured by 1 H-NMRS at a magnet strength of 1.5 tesla are N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), and lactate (Lac). NAA is a neuronal marker existing in normal, functioning neurons. It is thought to be present only in neuronal cell bodies, axons, and dendrites [6,7,8]. Reduced NAA is expected in tumors because it is primarily localized to healthy neurons [9,10] and thus, observed NAA is due to tumor infiltration of normal tissue.

METABOLITES:-
N-ACETYL ASPARTATE(NAA):-

N-acetyl aspartate (NAA) displays the huge peak of the spectra at 2.02 ppm as a singlet peak and additional quadruplet peak at 2.5 ppm.NAA is synthesised in the mitochondria and transported into neuronal cytoplasm. NAA is exclusively found in the CNS both gray and white matter. NAA is a marker of neuronal and axonal viability and density. Absence or decreased concentration of NAA is a sign of neuronal damage[11]. Central neurocytoma, an unusual neuronal tumor, have been stated to exhibit measurable NAA peak, although with reduced NAA/Cr[12].Increased NAA is nearly specified for canavan diseases. NAA is not demonstrated in meningioma and metastates. Like adult brain tumors, malignant pediatric brain tumors are characterized by an increase in the Cho: NAA ratio and a decrease in the NAA: Cr ratio, a general decrease in the NAA and Cr peaks, and an increase in Cho[13][14].
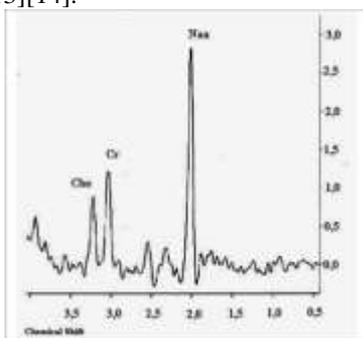
Fig 1:- A metabolite Peak of N-Acetyl Aspartate.

CREATINE(Cr):-

The peak of Cr spectrum is assigned at 3.02 ppm with chief contributions from creatine and phosphocreatine and slight contributions from GABA, lysine, and glutathione[15][16]. Cr is a marker of energetic systems and intracellular metabolism. Concentration of Cr is relatively constant. Cr is used as an internal reference for calculating metabolite ratio. Creatine is metabolise to creatinine which is excretedvia kidneys. However, literature proposes that glial tumors show 15–40% decrease in Cr levels. Related data has been reported in various other tumors as well, such as meningotheliomatousmeningiomas which displays about 20% decrease in total creatine[17][18]. Total creatine content is knowingly little in non-neuroectodermaltumors such as brain metastases related to neuroectodermaltumors.
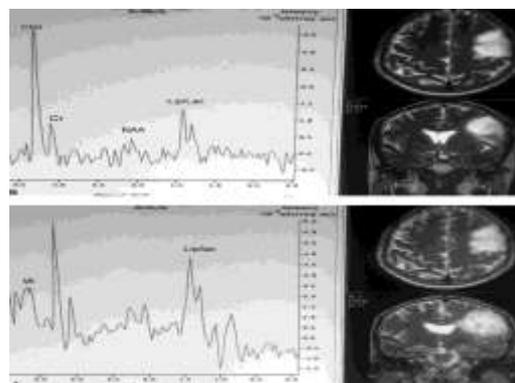
Fig2:-A metabolite peak of creatine

CHOLINE(CHO):-

Choline peak is assigned at 3.22 ppm and 3.52 ppm. The resonance is accredited to, phosphorylcholine (3.23 ppm),trimethyl ammonium residues of free choline (3.21 ppm),glycerophosphorylcholine (3.24 ppm) and other metabolites such as carnitine. Cho is a significant constituent of the Kennedy pathway, involved in genesis of phospholipid of the cell membranes. Cho is phosphorylated by Choline Kinase (CK) to from PCho which reacts additional with CTP to yield CDP-choline. Phosphatidylcholine (PC) then results from the reaction of CDPcholine with diacylglycerol[19]. The enzyme Choline Kinase is upregulated in several brain tumors and hence the existence of choline peak in MRS spectra reflects amplified cell membrane synthesis and thus amplified cellularity[20][21]. Cho peaks are raised in actively proliferating cells, as measured by phosphorous or proton magnetic resonance spectroscopic imaging, and in vivo proton magnetic resonance spectroscopic imaging proposes that Cho peaks associate with proliferative activity in gliomas[22]. Increase in choline may also be seen in infraction and inflammation.
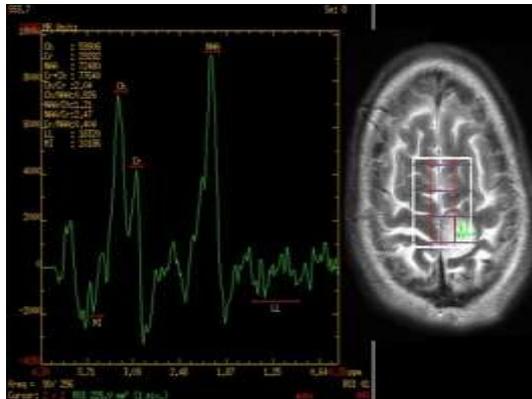
Fig3:- A metabolite peak of Choline

LACTATE(Lac):-
The peak of Lac is a doublet at 1.33 ppm. Peak of Lac is hardly seen in normal brain. Lac is a product of anaerobic metabolism such as cerebral hypoxia, ischemia, seizures , metabolic disorders (especially mitochondrial ones) macrophage accumulation (acute inflammation) tissues with poor washout such as cysts, necrotic and cystic tumors, normal pressure hydrocephalus. . Increased rates of lactate production are related with a range of tumors and usually implies higher tumor grade and relays with tumor metabolic activity. Lactate peak usually is lacking in low grade brain tumors and is component of classical MR spectroscopy sign for a high grade primary brain tumor[23].

MYO-INOSITOL (M-Ins):-
Myo is a simple sugar assigned between 3.56-3.57 ppm. Myo is a glial marker being primarily synthesized in astrocytes. Short TE H1 MRS is required for m-Ins visualization, but this metabolite can be seen, also with intermediate TEs, although to a lesser degree. Actually reducing the signal intensity by half; a second reduced peak (m-Ins2) is often detected at 4.05–4.06 ppm and can be used as another index of outstanding water suppression[24]. Myo may represent a product of myelin degradation. Myo is raised in gliosis, inflammation and in Alzheimer's diseases. Likewise, to tCho, m-Ins is described as an astroglial marker (sometimes increased in gliomas)[26] and as an osmolyte (reduced in hyponatremia and hepatic encephalopathy) ; it is also a component of neural receptor signaling systems, and its stages alteration[25][26].Myo may represent a product of myelin degradation.

LIPIDS:-
In the H1 MRS spectrum, the protons of the CH3 (methyl) groups of lipid molecules generate a minor peak at ~0.9 ppm, whereas protons of the CH2 (methylene) groups is responsible for the main peak at ~1.3 ppm[27]. Lipids are components of cell membranes not visualized on long TE. They are very short relaxation time. These peaks are absent in the normal brain. The presence of lipids may result from improper voxel selection. Lipid peak is seen in narcotic metastases and primary malignant tumors[28].
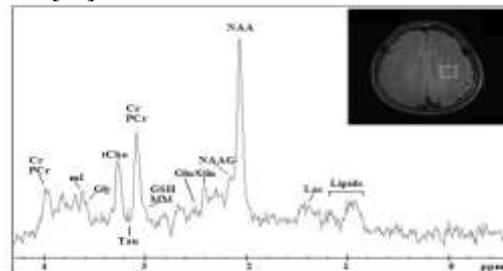
Fig 4:- This figure shows the peak of lipid

ALANINE(Ala):-
Ala is an amino acid that has a doublet centered at 1.48 ppm. This peak is located above the baseline in short TE and inverts on long TE. The peak may be obscured by Lac at 1.33 ppm in tumors, elevated level of Ala is specific for meningiomas[29].
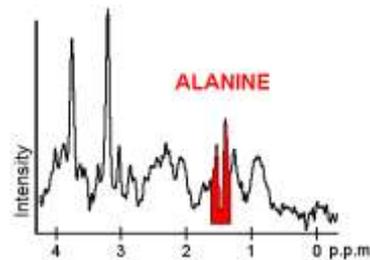
Fig 5:- This figure shows peak of alanine

1H SPECTROSCOPY DETECTION OF BRAIN TUMORS:-
GLIOMAS:-
The MR spectra of glioma mines exhibited characteristic changes according to the malignancy. NAA was visibly demonstrated in normal tissues, but its concentration was very low in glioblastomas. Total creatine concentrations decreased according to the malignancy. The concentrations of choline-containing compounds and inositol amplified with the malignancy, but declined with greater necrosis in glioblastomas. The MR spectra of glioblastomas presented tall peaks of glycine and alanine. Glycine in specific enlarged remarkably in glioblastomas regardless of

necrosis[30]. The glycine concentration was inversely related to NAA concentration, and the ratio of choline-containing com pounds to total creatine directly associated to glycine concentration, but decreased according to the extent of necrosis in glioblastomas.MR Spectroscopy, a 2*2cm voxel placed over the nodular portion of lesion, spectral waveform obtained at short TE of 35ms. Sharp doublet of lactate at 0.9 to 1.3ppm, short peaks suggestive of markedly reduced NAA at 2.02ppm and creatinine at 3.02ppm, sharply long peak of raised choline at 3.03ppm. There is a raised choline:creatinine ratio[31].

Fig 6:- This figure shows gliomas having reduced naa at 2.02 ppm creatinine at 3.02 ppm , sharply long peak of raised choline at 3.03ppm.

MENINGIOMA:-
The magnetic resonance spectra of Meningiomas exhibit enlarged choline (3.2 ppm) and reduced creatine (3.0 ppm). Alanine has been advised by various studies to be precise for meningiomas; however, different studies have reported adaptable occurrence rates [32]. A recent study shows that the alteration in reportable alanine levels might be due to the fact that alanine and lactate have very same resonance peaks (1.47 ppm versus 1.33 ppm) and may partially overlap, mainly at little magnetic field intensity. In cases where alanine levels are absent or ambiguous, glutamine/glutamate (Glu, 3.75 ppm), even if not a unique metabolite for meningioma, has been known as a potential additional metabolite to help identifymeningiomas[33][34].
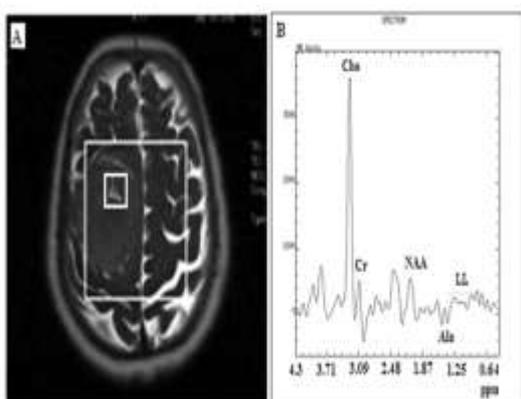
Fig 7:- This figure shows meningioma having the reportable alanine levels

OLIGODENDROGLIOMA:-
Magnetic resonance spectroscopy determines significantly higher cho and cho/crratio[35]. Higher incidence of lactate and lipid are seen in high grade than in low grade tumors. Low grade tumors may show highly raised cho simulating high grade tumors[36][37]. These tumors can have high cellular density but absent endothelial proliferation and necrosis. Glutamine and glutamate are significantly higher in low grade than in low grade astrocytoma[38][39].
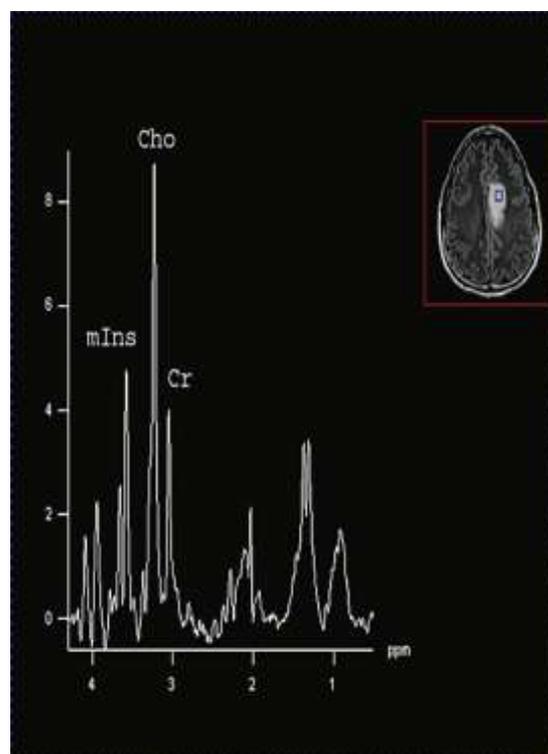
Fig 8:- This figure shows the significantly higher cho&cho/cr ratio

MEDULLOBLASTOMA:-
Medulloblastomas across molecular subgroups revealed distinct spectral features [40]. Group 3 and Group 4 tumors demonstrated metabolic profiles with readily detectable taurine, lesser levels of lipids, and high levels of creatine [41]. SHH tumors showed prominent choline and lipid with little levels of creatine and little or no evidence of taurine. A 5-metabolite subgroup classifier inclusive of creatine, myo-inositol, taurine, aspartate, and lipid 13a was developed that could distinguish between Group 3/4 and SHH medulloblastomas with excellent accuracy (cross-validated area under the curve [AUC] = 0.88) [42].
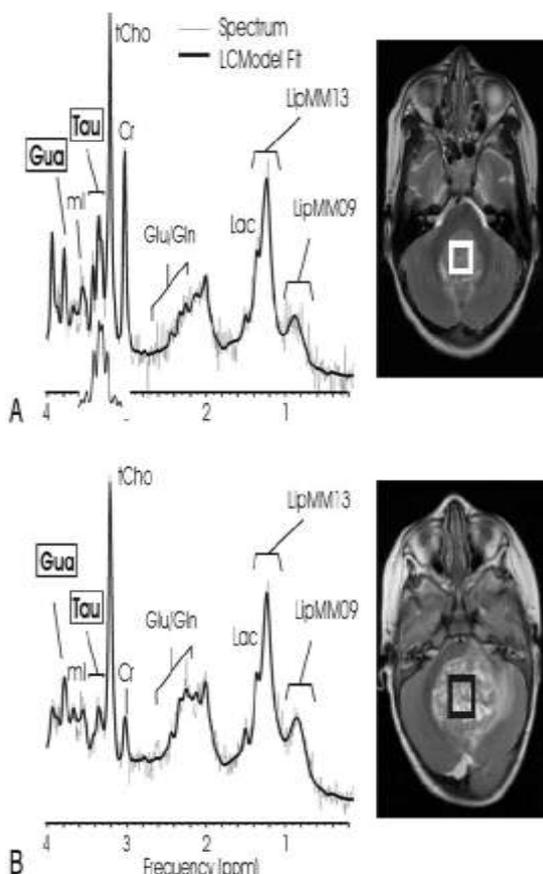
Fig 9:-This figure shows metabolic profiles with readily detectable taurine, lower levels of lipids, and high levels of creatine

II. RESULTS:-

Cho and Lipids and/or Lactate Peaks As Novel Magnetic Resonance SpectroscopicImaging BiomarkersforTumorEvaluation.This study investigates theutility ofproton magnetic resonance spectroscopic imaging in the identification of brain tumorbiomarkers and provides several significant conclusions for the utility of Cho andlipids and/or lactate, two noninvasive biomarkers, for the improved clinical evaluationof pediatric brain tumors. Importantly, these two biomarkers can serve as independentpredictors of tumor grade, and their combination can enhance pediatric brain tumorclassification. Tumor grading is essential for optimum therapy, especially for pediatricbrain tumors, which in contrast to adult brain tumors have better prognosis, but areoftensurgicallychallenging.AlthoughbothChoandlipidsand/orlactatehavepreviouslybeenassociatedwithtumorgrade,thisisthefirstanalysisoftheircombined utility for pediatric brain tumor assessment. This study also shows that theregion of the magnetic

resonance spectroscopic imaging spectrum that has the highestCho output strongly correlates with the pathological evaluation of the most malignantareas of tumor biopsy specimens, even in cases where the pathology and magneticresonance spectroscopic imaging resolutions are different. Thus, Cho analysis holdsthe promise of being able to direct biopsy to regions suitable for additional focaltherapy; the Cho and lipids and/or lactate peaks can serve as biomarkers to promotetreatment tailored to tumor behavior; a strong relationship exists between the levels ofthe magnetic resonance spectroscopic predictors and histopathological evaluation.

Forinstance,Choandlipidsand/orlactatepeaksarebothsignificantindependentpredictorsoftumorgradeandthereforecanandshouldbeincludedinfutureclassification systems of tumor grade. These conclusions are supported, in part, byprevious studies showing the potential of magnetic resonance spectroscopic imaging in the differential diagnosis and prognosis ofbraintumors.

III. CONCLUSION

Thisstudy concludedthattheMRspectroscopycouldprovideadditivevaluableinformation helping in brain lesions characterization that improved diagnosis and thusreducing unnecessary biopsies. Our results reveal that the MRS is an adequate tool forthe diagnosis of different brain lesions and tumors. Gliomas were the most commonbrainlesionsfoundinMRS.Moreover,thisstudyshowedthatthepresenceofdecreased in NAA peak in MRS is correlated with brain tumors. On the other hand,MRS tool has alimitation in the diagnosis of somebrain lesions.The techniqueisvery sensitive to inhomogeneity in the magnetic field and requires careful manualadjustment to ensure field uniformity. The most notable lesions, for which MRS aidedtheradiologistin offeringasinglediagnosis,werehigh-andlowgradegliomas,tuberculomas,cerebralinfarcts, recurrenttumours,andradiationnecrosis.MRScombinedwith MRI"improved"theimagingdiagnosisinmorethanhalf ofallpatients examined. MRS is also valuable in differentiating between recurrent tumourand radiation necrosis based on observing increased spectra of choline in recurrenttumours, along with increased Cho : NAA ratios and decreased NAA : Cr and NAA :Choratios.

CONFLICT OF INTEREST:
The authors declare no conflict of interest.

REFERENCES:-

[1]. Drost DJ, Riddle WR, Clarke GD. Proton magnetic resonance spectroscopy in the brain: report of AAPM MR Task Group #9. Med Phys 2002;29:2177-2197.

[2]. Pollack I. Brain tumors in children. N Engl J Med 1994;331:1500 –7.

[3]. Podo F. Tumour phospholipid metabolism. NMR Biomed 1999;12: 413–39.

[4]. . Ackerstaff E, Pflug BR, Nelson JB, Bhujwalla ZM. Detection of increased choline compounds with proton nuclear magnetic resonance spectroscopy subsequent to malignant transformation of human prostatic epithelial cells. Cancer Res 2001;61:3599 – 603.

[5]. Kwock L. Localized MR spectroscopy: basic principles. Neuroimaging Clin N. Am 1998;8:713-731.

[6]. Drost DJ, Riddle WR, Clarke GD. Proton magnetic resonance spectroscopy in the brain: report of AAPM MR Task Group #9. Med Phys 2002;29:2177-2197

[7]. Birken DL, Oldendorf WH. N-acetyl-L-aspartic acid: a literature review of a compound prominent in 1 H-NMR spectroscopic studies of brain. NeurosciBiobehav

[8]. Simmons ML, Frondoza CG, Coyle JT. Immunocytochemical localization of N-acetyl-aspartate with monoclonal antibodies. Neuroscience 1991;45:37-45

[9]. Tallan HH. Studies on the distribution of N-acetyl-L-aspartic acid in brain. J BiolChem 1957;224:41–5.

[10]. Koller KJ, Zaczek R, Coyle JT. N-Acetyl-aspartyl-glutamate: regional levels in rat brain and the effects of brain lesions as determined by a new HPLC method. J Neurochem 1984;43:1136 – 42.

[11]. C. A. Davie, C. P. Hawkins, G. J. Barker, A. Brennan, P. S. Tofts, D. H. Miller, W. I. McDonald, Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions, Brain, Volume 117, Issue 1, February 1994, Pages 49–58, https://doi.org/10.1093/brain/117.1.49.

[12]. Chuang, Ming-Tsung MD[*]; Lin, Wei-Chen MD[*]; Tsai, Huei-Yi MD[*]; Liu, Gin-Chung MD[*]; Hu, Shih-Wen MD[†]; Chiang, I-Chan MD[*] 3-T Proton Magnetic Resonance Spectroscopy of Central Neurocytoma, Journal of Computer Assisted Tomography: September 2005 - Volume 29 - Issue 5 - p 683-688 doi: 10.1097/01.rct.0000171240.95430.29

[13]. Sutton LN, Wang Z, Gusnard D et al. Proton magnetic resonance spectroscopy of pediatric brain tumors. Neurosurgery 1992;31:195-202.

[14]. Tzika AA, Vajapeyam S, Barnes PD. Multivoxel proton MR spectroscopy and hemodynamic MR imaging of childhood brain tumors: preliminary observations. Am J Neuroradiol 1997;18:203-218.

[15]. R. Kreis ,B.D. Ross , Cerebral metabolites disturbances in patients with subacute and chronic diabetes mellitus: detection with proton MR spectroscopy , Radiology 184 (1992) 123-130.

[16]. R. Kreis ,B.D. Ross , N.A. Farrow , Z. Ackerman , Metabolic disorder of brain in chronic encephalopathy detected with H-1 MR MR spectroscopy , Radiology 182 (1992) 19-27.

[17]. Y.Kinoshita , A. Yokota ,absolute concentrations of metabolites in human brain tumors using in vitro proton magnetic resonance spectroscopy ,NMR Biomed. 10 (1) (1997)2-12.

[18]. O.H. Lowry , S.J. Berger , M.M.Y.Chi, A. Blackshaw, W. Outlaw , Diversity of metabolic patterns in human brain tumors. I.High energy phosphate compounds and basic compostion, J. Neurochem. 29(1977) 959-977.

[19]. TrivediDevanshi G; ChaudharyAnkit B; Patel Bhoomi D. Method Development and Validation for Estimation of Clotrimazole, Fusidic acid and MometasoneFuroate in Cream by RP-HPLC, World Journal of Pharmacy and Pharmaceutical Sciences. 2017 April;

6(5): 1204-1219. DOI: 10.20959/wjpps20175-9173.

[20]. B.L. Miller, L. Chang, R. Booth, et al., In vivo 1H MRS choline: correlation with in vitro chemistry/histology, Life Sci. 58 (1996) 1929–1935.

[21]. L. Chang, D. McBride, B.L. Miller, et al., Localized in vivo 1H magnetic resonance spectroscopy and in vitro analyses of heterogeneous brain tumors, J. Neuroimaging 5 (1995) 157–163.

[22]. Tamiya T, Kinoshita K, Ono Y, Matsumoto K, Furuta T, OhmotoT.Proton magnetic resonance spectroscopy reflects cellular proliferative activity in astrocytomas. Neuroradiology 2000;42:333– 8.

[23]. M.E. Mullins, MR spectroscopy: truly molecular imaging; past,present and future, Neuroimaging Clin. N. Am. 16 (4) (2006) 605–618.

[24]. Danielsen ER, Ross B. Magnetic Resonance Spectroscopy Diagnosis of Neurological Diseases. New York: Marcel Dekker, Inc., 1999.

[25]. Lehnhardt FG, Röhn G, Ernestus RI, et al. 1 H- and (31) P-MR spectroscopy of primary and recurrent human brain tumors in vitro: malignancy-characteristic profiles of water soluble and lipophilic spectral components. NMR Biomed 2001;14:307-17.

[26]. Patel B. Patel M. Chaudhary A. A Comprehensive and Comparative Study on Regulations of Medical Countermeasures in USA and INDIA. International Journal of Emerging Technologies and Innovative. 2019 May; 6(5): 289-304.

[27]. Patel BK. Chaudhary AB. Bhadani SM. Patel BD. Development and validation of stability indicating RP-HPLC method for simultaneous estimation of Aceclofenac and Cyclobenzaprine Hydrochloride in pharmaceutical dosage from. World Journal of Pharmacy and Pharmaceutical Sciences, 2018 April; 7(5): 874-888.

[28]. Patel DM. Chaudhary AB and Patel BD. Development and validation of RP-HPLC method for simultaneous estimation BeclomethasoneDipropionate, Phenylephrine Hydrochloride and Lignocaine Hydrochloride in cream. World Journal of Pharmacy and

Pharmaceutical Sciences. 2018 April; 7(5): 829-841.

[29]. Choi C, Ganji SK, DeBerardinis RJ, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012;18:624-9.

[30]. Shimizu H, Kumabe T, Shirane R, Yoshimoto T. Correlation between choline level measured by proton MR spectroscopy and Ki-67 labeling index in gliomas. AJNR Am J Neuroradiol 2000;21:659 – 65

[31]. Duyn JH, Frank JA, Moonen CT. Incorporation of lactate measurement in multi-spin-echo proton spectroscopic imaging. MagnReson Med 1995;33:101–7.

[32]. Patel BD. Bhavya M, Ankit BC. Method Development and Validation For Simultaneous Estimation of Lamivudine and Zidovudine in Tablet by Reverse-Phase High-Performance Liquid Chromatography. Asian Journal of Pharmaceutical and clinical Research. 2020 June; 13(6): 73-77.

[33]. Patel BD, Chaudhary AB, Parmar PJ, Patel VN. Development and validation of reversed phase high performance liquid chromatography method for simultaneous estimation of NebivololHCl and Cilnidipine in combined tablet dosage form. Pharm. and Bio. Eval. (2016); 3(2): 208-214.

[34]. Bhoomi DP, Nidhi JD, Ankit C. Development and Validation of RP-HPLC Method for Estimation of Teneligliptin and its Impurity in Tablet. International Journal of Pharmaceutical Sciences Review and Research, 2021 August; 69(2): 127-133.

[35]. Gillies RJ, Barry JA, Ross BD. In vitro and in vivo 13C and 31P NMR analyses of phosphocholine metabolism in rat glioma cells. MagnReson Med 1994;32:310 – 8.

[36]. Patel BD, Chaudhary A, Gami S, "RP-HPLC Method Development and Validation for Simultaneous Estimation of Benidipine Hydrochloride, Telmisartan and Chlorthalidone in Tablet" Journal of Emerging Technologies and Innovative Research. 2019; 6(3): 110-124.

[37]. Fulham MJ, Bizzi A, Dietz MJ, Shih HH, Raman R. Mapping of brain tumor metabolites with proton MR spectroscopic

imaging: clinical relevance. Radiology 1992;185:675– 86.

[38]. Veale MF, Roberts NJ, King GF, King NJ. The generation of 1H-NMR-detectable mobile lipid in stimulated lymphocytes: relationship to cellular activation, the cell cycle, and phosphatidylcholinespecific phospholipase C. BiochemBiophys Res Commun 1997;239: 868 –74.

[39]. Griffin JL, Lehtimaki KK, Valonen PK, et al. Assignment of 1H nuclear magnetic resonance visible polyunsaturated fatty acids in BT4C gliomas undergoing ganciclovir-thymidine kinase gene therapy-induced programmed cell death. Cancer Res 2003;63:3195–201.

[40]. De Stefano N, Caramanos Z, Preul MC, Francis G, Antel JP, Arnold DL. In vivo differentiation of astrocytic brain tumors and isolated demyelinating lesions of the type seen in multiple sclerosis using 1H magnetic resonance spectroscopic imaging. Ann Neurol 1998;44:273– 8.

[41]. Majos C, Alonso J, Aguilera C, et al. Adult primitive neuroectodermaltumor: proton MR spectroscopic findings with possible application for differential diagnosis. Radiology 2002;225:556.

[42]. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. ClinChem 1993;39:561–77.