ISSN: 2456-043X
International Journal of Engineering Science and Generic Research (IJESAR)
Available Online at www.ijesar.in
Journal Index In ICI World of Journals - ICV 2016 – 68.35
Volume 9; Issue 2; March-April; 2023; Page No. 18-26

Aniracetam and Related Impurities in Bulk Drug: Development and Validation of Stability Indicating Reversed-Phase HPLC Purity Method

Indu Kumari [*1], Dr. Nagendra Pratap Mishra [2]

[1]Research Scholar, Sunrise University, Alwar

[2]Professor, Sunrise University, Alwar

Abstract

A strong semi-synthetic antiparasitic medication used in veterinary medicine is ivermectin. It is often used to treat parasites. In order to test and identify ivermectin, as well as to identify and estimate its associated compounds in bulk drug substance batches of ivermectin, this research set out to create a stability-indicating reversed-phase HPLC (RP-HPLC) approach. The goal of this project is to create a method for employing reversed-phase liquid chromatography to separate and measure aniracetam and associated contaminants in bulk medication. In order to ensure consistent quality control analyses and (tR)Retention time for related impurities, this approach is employed in the manufacture of aniracetam. The International Conference on Harmonization (ICH)'s Q1A (R2) and Q2 (R) were followed throughout the validation procedure. The HPLC technique was successfully designed, verified, and shown to be accurate, robust, specific, and stable suggesting for the analysis of ivermectin and estimate of its associated chemicals.

KEYWORD: Aniracetam, Impurities, Bulk Drug Development and Hplc Purity Method

INTRODUCTION

The Indian pharmaceutical industry has come a long way since its start in 1975, and is now the most diverse and vertically integrated in the developing world. The nation now produces its own pharmaceutical formulations and a significant portion of its own bulk medications. Imports of 49 bulk pharmaceuticals totaled a minimal Rs.10.17 crores in 1984-85, accounting for less than 0.5% of total formulation output in the nation. Technologies for the production of several bulk drugs, including antibiotics like Ampicillin, Amoxycillin, Erythromycin, Anti-infectives like Sulphamethaxazole and Trimethoprim., anti-TB drugs like Ethambuto Cardio Vascular drugs like Methyl Dopa; Analgesics like Ibuprofen and Isopropyl antipyrine; anti - amoebics like Metronidazole and Tinidazole, anti-cancer drugs like Vinblastine, Vincristire and Cisplatin were indigenously developed. The trade balance in the pharmaceutical industry has improved as exports have increased. In 1984–85, the international trade in pharmaceuticals and pharmaceutical formulations was Rs.217.49 crores (or about $215 million). The United States and Western European nations are among the several that get these pharmaceutical exports. Some Indian companies provide turnkey plants and technical services, while others have built up manufacturing facilities in foreign nations. In order to achieve the goals of the National Health Policy and maximize export potential, the Indian Pharmaceutical Industry's diverse manufacturing and technological skills are essential instruments.

It is crucial to provide the Indian Pharmaceutical Industry a technical and productivity impetus that would also allow it to exploit export potential, since medicine prices are partly dictated by the cost effectiveness of local manufacturing. Promoting competition and economic scales of production, as well as reducing needless impediments to expansion, would best serve the

purpose of assuring plentiful supply of medications at affordable rates. This is why there is more leeway in the approval and licensing processes for important and life-saving pharmaceuticals. The data from the last several years' worth of bulk production pricing on the market has already confirmed the veracity of this assumption. However, the government will keep a close eye on FERA firms to make sure they are in line with national goals and aspirations.

LITERATURE REVIEW

van der Gronde, Toon & Pieters, Toine. (2018). Just So You Know Prasad and Mailankody1 presented an Original Investigation in the most recent issue of JAMA Internal drug that examines the costs involved with bringing a single drug with an oncological indication to market. After analyzing data from 10 businesses, they determined that the average cost to create a medicine was $648 million, whereas the average income after four years was $1,658,400,000. This adds fuel to the fire that pharmaceutical medicine pricing have little relation to the true expenses of R&D, and that big bucks may be gained from the drug industry

Oke, Emmanuel. (2022). This article compares and contrasts the legal solutions to the tension between the right to health and pharmaceutical patent rights in Kenya, South Africa, and India. This research begins by analyzing the human right to health in the context of patent rights. The paper then analyzes the legal standing of the right to health in Kenya, South Africa, and India. The paper also analyzes the judicial decisions made on pharmaceutical patent problems in these three developing countries where the right to health and patent rights were at conflict with one another. The paper contends that the incorporation of the right to health into the adjudication of patent disputes might significantly contribute to the availability of affordable medicines in developing nations..

Celia, et.al. (2020). The analytical methods for determining Literature from a variety of analytical and pharmaceutical chemistry publications, as well as reviews of bulk drug, formulation, and biological fluid COX-2 inhibitors, have been surveyed. From 1995 to 2004, a total of 138 different analytical methods, such as spectrophotometric and chromatographic approaches, were described, and this overview includes all of them. More than a hundred different procedures were developed, and many of them relied on LC and UV detection, but it turned out that the vast majority of people used HPLC with UV detection. Current state-of-the-art analytical techniques for the detection of celecoxib, rofecoxib, etoricoxib, etodolac, nimesulide, and meloxicam have been reviewed and analyzed.

Mullett, Wayne. (2017). The pharmaceutical sector is presently facing a major challenge related to the management of pharmaceutical contaminants. The International Conference on Harmonization (ICH) has created a reliable standard for the control of pollutants.. This overview describes various impurities, where they come from, and how they degrade, with reference to the ICH rules and some concrete instances. Methods for limiting the presence of contaminants in medications are also discussed.

Ağın, Fatma & ATAL, Sena. (2019). Objectives: The electro-oxidation behavior of the non-steroidal anti-inflammatory drug tenoxicam (TX) on a multiwalled carbon nanotube (MWCNT)-modified glassy carbon electrode (GCE) was investigated using cyclic voltammetry, differential pulse voltammetry, and square wave voltammetry. Materials and methods: The GCE was modified with MWCNT to allow for sensitive voltammetric measurement of TX. TX peak current was about 0.520 V for DPV and 0.570 V for SWV when the potential was scanned in a positive direction. Diffusional control over the irreversibility of TX oxidation was shown. Obtaining linear responses in the range of 2107-1105 M for DPV with a limit of detection (LOD) of 1.43109, and in the region of 8109-8106 M for SWV with a LOD of 9.971010, respectively. Authors report positive results from determining TX in a medicinal dose form utilizing fully verified DPV and SWV.

RESEARCH METHODOLOGY

Substances and Techniques:

Equipment and programming:

For this specific training and chromatographic separation, an Agilent HPLC 1100 series with a diole array detector (DAD) microprocessor,

quaternary pump, and a variable wavelength detector (VWD) was utilized, and an Eclipse XDB C18 (150mm4.6mm5m) column was utilized as the stationary phase with a binary gradient.

Chemicals and reagents:

The experimental solvents included acetonitrile, ortho phosphoric acid (85%, AR grade), methanol (HPLC), and water.

Standards and sample materials:

Pharmacies rely on high-purity compounds like aniracetam (99.9%), 4-methoxy benzoic acid (99.9%), N-anisoyl GABA (99.9%), and 2-pyrrolidinone (99.9%). The analysis also made use of several compounds, all of which were of analytical quality.

Preparation of solutions:

Diluted standard solution:

Carefully measure 500 milligrams of aniracetam into a 100-milliliter volumetric flask. Sonication was used to help dissolve the contents of the flask before they were diluted with 50 mL of diluent and brought to the proper amount. Here is a sample solution at 5000 ppm.

Impurity stock solution:

First, in a 50 mL volumetric flask, I carefully weighed 500 mg of 4-methoxy benzoic acid. The contents were sonicated to dissolve, then the flask was filled with diluent to the correct volume and the mixture was well stirred. This solution's sample size was 10,000 ppm.

2. After careful weighing and measuring, 500 milligrams of N-anisoyl GABA were added to a 50-milliliter volumetric flask. The contents were sonicated to dissolve, then the flask was filled with diluent to the correct volume and the mixture was well stirred. This solution's sample size was 10,000 ppm.

3. prepared a 50 mL volumetric flask by transferring 500 mg of 2-pyrrolidinone from a weighing scale. Sonicated until contents were dissolved, then added enough diluent to fill flask to the correct volume and stirred well. The concentration of the fluid sampled was 10,000 ppm.

Standard stock solution:

The reference standard, aniracetam, was transferred carefully from a 500mg vial to a 100mL volumetric flask under a precision balance. Twenty-five milliliters of impurity (1 stock solution), twenty-five milliliters of impurity (3 stock solutions), and twenty-five milliliters of impurity (2 stock solutions) were added to the flask. The ingredients were dissolved using sonication, and the volume was adjusted using diluent. This solution included 5000 ppm of aniracetam together with 2500 ppm of 4-methoxy benzoic acid, 2 pyrrolidinone, and N-anisoyl GABA.

Resolution and system suitability solution (Test solution):

The standard stock solution was diluted and mixed well after a 10.0 mL aliquot was transferred to a 100 mL volumetric flask. This concoction included 500 ppm of aniracetam, 250 ppm of 4-methoxy benzoic acid, 250 ppm of 2-pyrrolidinone, and 250 ppm of N-anisole GABA.

DATA ANALYSIS

Optimization of chromatographic conditions:

Because of their importance in quality control, analytical research has been increasingly focused on improving HPLC methods for identifying chemicals. Because of how simple it is to implement; the strategy has attracted widespread adoption among academics. The primary objective of developing a drug synthesis process is to establish a quantitative relationship between drug and drug intermediate yields. Eclipse XDB C18 (150mm4.6mm5m) or an analogous column was chosen for the development of the approach proposed because 2-pyrrolidinone, one of the components, is a polar molecule that necessitates an aqueous mobile phase. Since 2-pyrrolidinone is extremely polar, 4-methoxy benzoic acid and N-anisoyl GABA are acidic, and aniracetam is somewhat non-polar, a gradient elution was required. If the pH of the mobile phase is less than 2, the acidic compounds 4-methoxy benzoic acid and N-anisoyl GABA will co elute and migrate to the left of the chromatogram, whereas if the pH is more than 2, they will move closer to the aniracetam peak. Finally, it was determined that a

linear gradient program beginning with the preparation of mobile phase-A—0.02 M ortho phosphoric acid (H3PO4) in water, filtration through a 0.45 m membrane, and sonication to degas—was the best method for adequate retention of 2-pyrrolidinone and acceptable separation of the five compounds. Acetonitrile was used to make the mobile phase-B.. Maximum wavelength (max) absorbance of the important chemicals is used to drive detector wavelength variation during analysis. Below 220 nm, 2-pyrrolidinone was very absorbent.

Method validation:

In accordance with ICH recommendations and using bulk drug standards, the devised technique is validated for the identification of aniracetam and three contaminants. Thus, the system's suitability, as well as the method's The analytical limits of detection and quantification for all three impurities, as well as their selectivity, specificity, linearity, range, precision (repeatability), intermediate precision, accuracy, short-term and long-term stability of the analyzers in the ready solutions, and robustness, have all been demonstrated.

System suitability:

The method was put to the test by creating a mixed standard solution of aniracetam and the three contaminants (diluted in diluent and contained each component at a concentration level of 0.5mg/mL). Validity of the analytical technique relies heavily on the results of the system appropriateness test. To that end, important metrics such as aniracetam retention time (tR), peak area (A), Resolution (RS) between adjacent peaks and relative retention time (RtR) were measured and tracked daily. The essential parameters of RS satisfied the acceptance requirements of RS1.5 and ensured for satisfactory separation quantification during the validation of the technique.

Selectivity:

Selectivity is measured Active Pharmaceutical Ingredient (API) purity may be determined by monitoring the chromatograms of a blank sample into which the API has been deliberately introduced while all diluent, bulk drug, and formulation contaminants are present. Since a suitable placebo solution was not available for this work, Each excipient's solution series was used in the verification process. Under the optimum chromatographic settings, there was sufficient resolution (RS>3.2) between the neighboring peaks of aniracetam and the three contaminants (2-pyrrolidinone, 4-methoxy benzoic acid, N-anisoyl GABA, aniracetam). Reliable quantification of 2-pyrrolidinone was confirmed by a critical resolution of higher than 3.2 between 2-pyrrolidinone and early eluted peaks at dead volume.

Study of linearity and range:

Aniracetam and three related contaminants are characterized analytically by describing factors of typical standard calibrating curves. Aniracetam calibration curves all have R2 values over 0.9999 for all contaminants tested (4-methoxy benzoic acid, N-anisoyl GABA, and 2-pyrrolidinone); for all but 2-pyrrolidinone impurity, Y- Intercept 25%, where x is the calculated response at the concentration of the specification limit. All calibration curves were subjected to a goodness-of-fit test, with the results shown in Tables 4.2–4.5, along with the R2 values obtained for typical curves System suitability limitations were satisfied at the 96% confidence level as follows: 0.999 for aniracetam, 0.991 for 2-pyrrolidinone, 0.999 for 4-methoxy benzoic acid, and 0.998 for N-anisoyl GABA aniracetam. Aniracetam concentration vs peak area yielded eight distinct levels (corresponding to concentrations of 0.5% to 150% of the test solution) by plotting aniracetam against all contaminants across the range of 0.75-0.0025mg/mL. Aniracetam, N-Acetyl-GABA, 2-Pyrrolidinone, and 4-Methoxybenzoic Acid all had regression equations of the form Y= 172.1 +24.04, Y= 87.97 -5.354, Y= 112.8 -155.4, and Y= 90.88 +357.7,

Table-1: Linearity and range for aniracetam.

Sr.no.	Linerity % level	mg/mL	ppm	Area
1	0.5	0.0025	2.5	87
2	1	0.005	5	176
3	2	0.01	10	353
4	5	0.025	25	873
5	10	0.05	50	1564
6	20	0.1	100	3497
7	40	0.2	200	6944
8	50	0.25	250	8625
9	75	0.375	375	13273
10	100	0.5	500	17414
11	125	0.625	625	21307
12	150	0.75	750	25751

Table-2: Linearity and range for impurity 4-methoxy benzoic acid.

Sr.no.	Linerity % level	mg/mL	ppm	Area
1	0.5	0.00125	1.25	52
2	1	0.0025	2.5	94
3	2	0.005	5	201
4	5	0.0125	12.5	458
5	10	0.025	25	814
6	20	0.05	50	1746
7	40	0.1	100	3508
8	50	0.125	125	4350
9	75	0.1875	187.5	6651
10	100	0.25	250	8828
11	125	0.3125	312.5	10861
12	150	0.375	375	13266

Correlation: 0.999

Table-3: Linearity and range for impurity 2-pyrrolidinone.

Sr.no.	Linerity % level	mg/mL	ppm	Area
1	0.5	0.00125	1.25	51
2	1	0.0025	2.5	106
3	2	0.005	5	203
4	5	0.0125	12.5	338
5	10	0.025	25	1309
6	20	0.05	50	3168
7	40	0.1	100	4610
8	50	0.125	125	5257
9	75	0.1875	187.5	7039
10	100	0.25	250	9526
11	125	0.3125	312.5	11024
12	150	0.375	375	15941

Correlation: 0.991

Table-4: Linearity and range for impurity N-anisoyl GABA.

Sr.no.	Linerity % level	mg/mL	ppm	Area
1	0.5	0.00125	1.25	107
2	1	0.0025	2.5	164
3	2	0.005	5	241
4	5	0.0125	12.5	554
5	10	0.025	25	1015
6	20	0.05	50	1972
7	40	0.1	100	4025
8	50	0.125	125	5132
9	75	0.1875	187.5	7882
10	100	0.25	250	11200
11	125	0.3125	312.5	14064
12	150	0.375	375	18005

Correlation: 0.998

Precision study:

To demonstrate repeatability and intermediate precision, we reported each analyte concentration with aniracetam as a percentage relative standard deviation (% RSD). For a data level of 100% and LOQ measured from over calculation, the signal-to-noise ratio is satisfactory. Then, six replicates of the 100% LOQ and 100% LOQ solutions were injected to ensure accuracy. Assuming the accuracy of the above estimate, Six-injection LOQ and 100% response RSDs shouldn't be more than 10%. Learning at an intermediate level of accuracy allows for the exchange of information across laboratories on a day other than the day originally planned.

Table-5: Summary of precision study of aniracetam and impurity (4-methoxy benzoic acid) 100% level of Day-1.

Preparation	Aniracetam	Impurity(4-methoxy benzoic acid)
	Area	Area
1	17423	8884
2	17325	8902
3	17337	8867
4	17257	8785
5	17427	8894
6	17386	8859
Mean	17359	8865
SD	65.563	42.452
% RSD	0.38	0.48

Table-6: Summary of precision study of aniracetam and impurity (4-methoxy benzoic acid) at 100% level of Day-2.

Preparation	Aniracetam	Impurity(4-methoxy benzoic acid)
	Area	Area
1	17427	8884
2	17327	8766
3	17425	8914
4	17220	8847
5	17418	8763
6	17314	8828
Mean	17355	8834
SD	83.35	61.269
% RSD	0.48	0.69

Table-7: Summary precision for aniracetam and (2-Pyridinone-4-Methoxybenzoic Acid-N-Acetyl Glutamic Acid impurity) at LOQ.

Day-1				
Preparation	Aniracetam	Impurity (4-methoxy benzoic acid)	Impurity (2-pyrrolidinone)	Impurity (N-anisoyl GABA)
	Area	Area	Area	Area
1	709	292	2520	520
2	702	315	2480	480
3	705	283	2495	544
4	702	315	2512	509
5	705	283	2560	510
6	709	292	2488	500
Mean	705	297	2509	511
SD	3.14	14.76	29.01	21.24
% RSD	0.45	4.98	1.16	4.16

Study of accuracy (recovery):

The precision of an analytical method is measured by how near its test findings approximate the real worth. In a perfect world, the value that was really measured would have been the true one.

An aniracetam powder test solution with a nominal concentration of 0.5mg/mL of aniracetam and contaminants was created as the first solution in a level four solution for the estimate of powder recovery. Similar recovery studies were performed on a powdered combination of the bulk medication and the regular addition procedure.

Aniracetam and all other contaminants were spiked into a sample at 50%, 100%, and 150% of the intended concentration to prove the reliability of the testing procedure. Each tier had three sets made. We measured the % recovery by injecting these solutions into the chromatographic equipment and recording the area of the impurity peak at each concentration. Both the bulk medication and the powder formulation underwent recovery trials using the conventional addition technique. Standard addition technique slopes were statistically similar to those of the standard calibration curves. Aniracetam has been shown to have recovery values between 98.10% and 98.98%, 2-pyrrolidinone between 97.86% and 98.92%, 4-methoxy benzoic acid between 99.54% and 100.31%, and N-anisoyl GABA between 98.01% and 99.0%. The RSD from all three sets was below NMT 10.0, hence the system's appropriateness parameters were fulfilled. Tables 4.9 and 4.10, of the chromatogram, detail the study findings for the bulk medication and impurities that met the acceptable standards for accuracy.

Table-8: Summary of accuracy (recovery) standard sample of Aniracetam and 4-methoxy benzoic acid.

Drug name	Recovery level	Set No.	Mean Area	Amount Added (µg/mL)	Amount Found (µg/mL)	Recovery%	Mean Recovery (%)	SD	RSD %
Aniracetam	50%	Set 1	8615	250.1	247.36	98.90	98.94	0.04	0.04
		Set 2	8610	249.9	247.21	98.93			
		Set 3	8625	250.2	247.65	98.98			
	100%	Set 1	17210	500.1	494.14	98.81	98.59	0.32	0.32
		Set 2	17101	499.9	491.01	98.22			
		Set 3	17201	500.2	493.88	98.74			
	150%	Set 1	25650	750.1	736.48	98.18	98.17	0.07	0.08
		Set 2	25620	749.9	735.62	98.10			
		Set 3	25669	750.2	737.02	98.24			
4 benz oic acid	50%	Set 1	4401	125.1	124.63	99.63	99.75	0.30	0.30
		Set 2	4390	124.9	124.32	99.54			
		Set 3	4425	125.20	125.31	100.09			
	100%	Set 1	8801	250.20	249.24	99.61	99.69	0.07	0.07
		Set 2	8799	249.9	249.18	99.71			
		Set 3	8810	250.1	249.49	99.76			
	150%						99.92	0.35	0.35
		Set 2	13190	374.9	373.53	99.63			
		Set 3	13290	375.2	376.36	100.31			

Table-9: Summary of accuracy (recovery) standard sample of 2-pyrrolidinone, N-anisoyl GABA.

Drug name	Recovery level	Set No.	Mean Area	Amount Added (µg/mL)	Amount Found (µg/mL)	Recovery %	Mean Recovery (%)	SD	RSD %
2-pyrrolidinone	50%	Set 1	4680	124.8	122.82	98.41	98.27	0.36	0.37
		Set 2	4650	124.7	122.03	97.86			
		Set 3	4701	125.20	123.37	98.54			
	100%	Set 1	9410	250.1	246.96	98.74	98.69	0.12	0.12
		Set 2	9380	249.8	246.17	98.55			
		Set 3	9420	250.3	247.22	98.77			
	150%	Set 1	14001	374.8	367.44	98.04	98.57	0.47	0.48
		Set 2	14120	375.2	370.56	98.76			
		Set 3	14150	375.4	371.35	98.92			
N-anisoyl GABA	50%	Set 1	5556	125.3	124.02	98.98	98.61	0.52	0.53
		Set 2	5480	124.8	122.32	98.01			
		Set 3	5540	125.10	123.66	98.85			
	100%	Set 1	11001	249.7	245.56	98.34	98.67	0.30	0.31
		Set 2	11090	250.2	247.54	98.94			
		Set 3	11050	249.8	246.65	98.74			
	150%	Set 1	16480	374.8	367.86	98.15	98.64	0.44	0.45
		Set 2	16600	375.1	370.54	98.78			
		Set 3	16650	375.4	371.65	99.00			

CONCLUSION

An innovative to determine Aniracetam and its three related impurities, 4-Methoxy benzoic acid, N-anisoyl GABA, and 2-pyrrolidinone, simultaneously in the bulk drug, synthesis drug, drug intermediate, and tablet formulation, a reversed-phase high performance liquid chromatography method was developed, validated, and shown to be sensitive, accurate, precise, and robust. The first method for routine analysis and quality control of Aniracetam in relevant forms has been established., and it has been published in the scientific literature. Aniracetam, it seems, can be broken down into its precursor in alkaline conditions. We used infrared

(IR), High-Performance Liquid Chromatography (HPLC) with Nuclear Magnetic Resonance (1H NMR) to detect and characterize these degradation products. Regular examination of aniracetam and related substances may benefit from this HPLC technique as well. Aniracetam's alkaline breakdown and other degradation routes are discussed.

REFERENCES

1. van der Gronde, Toon & Pieters, Toine. (2018). Assessing Pharmaceutical Research and Development Costs. JAMA Internal Medicine. 178. 587. 10.1001/jamainternmed.2017.8706.
2. Oke, Emmanuel. (2022). The Right to Health in Pharmaceutical Patent Disputes (South Centre Research Paper No. 145).
3. Celia, Christian & Di Marzio, Luisa & Locatelli, Marcello & Ramundo, Piera & D'Ambrosio, Francesca & Tartaglia, Angela. (2020). Current Trends in Simultaneous Determination of Co-Administered Drugs. Separations. 7. 10.3390/separations7020029.
4. Mullett, Wayne. (2017). Determination of drugs in biological fluids by direct injection of samples for liquid-chromatographic analysis. Journal of biochemical and biophysical methods. 70. 263-73. 10.1016/j.jbbm.2006.10.001.
5. Ağın, Fatma & ATAL, Sena. (2019). Electroanalytical Determination of the Antiinflammatory Drug Tenoxicam in Pharmaceutical Dosage Forms. Turkish Journal of Pharmaceutical Sciences. 16. 184-190. 10.4274/tjps.galenos.2018.60783.
6. Parvatker, Abhijeet & Tunceroglu, Huseyin & Sherman, Jodi & Coish, Philip & Anastas, Paul & Zimmerman, Julie & Eckelman, Matthew. (2019). Cradle-to-Gate Greenhouse Gas Emissions for Twenty Anesthetic Active Pharmaceutical Ingredients Based on Process Scale-Up and Process Design Calculations. ACS Sustainable Chemistry & Engineering. 7. 10.1021/acssuschemeng.8b05473.
7. Stegemann, Sven & Klebovich, Imre & Antal, Istvan & Blume, Henning & Magyar, Kálmán & Németh, György & Paal, Tamas & Stumptner, Willibald & Thaler, György & Putte, Armand & Shah, Vinod. (2011). Improved therapeutic entities derived from known generics as an unexplored source of innovative drug products. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences. 44. 447-54. 10.1016/j.ejps.2011.09.012.
8. Yoo, Seung-Lai & Kim, Dae-Jung & Lee, Seung-Mi & Kang, Won-Gu & Kim, Sang-Yoon & Lee, Jong & Suh, Dong-Churl. (2019). Improving Patient Access to New Drugs in South Korea: Evaluation of the National Drug Formulary System. International Journal of Environmental Research and Public Health. 16. 288. 10.3390/ijerph16020288.
9. Suri, F. & Banerji, Amit. (2016). Super Generics--First Step of Indian Pharmaceutical Industry in the Innovative Space in US Market. Journal of Health Management. 18. 10.1177/0972063415625566.
10. Weitzel, Jane & Pappa, Horacio & Banik, Gregory & Barker, Amy & Bladen, Elizabeth & Chirmule, Narendra & DeFeo, Joseph & Devine, Jennifer & Emrick, Steven & Hout, Taha & Levy, Michael & Mahlangu, Gugu & Rellahan, Barbara & Venema, Jaap & Workman, Wesley. (2021). Understanding Quality Paradigm Shifts in the Evolving Pharmaceutical Landscape: Perspectives from the USP Quality Advisory Group. The AAPS Journal. 23. 10.1208/s12248-021-00634-5.
11. Diab, Samir & McQuade, D. & Gupton, B. & Gerogiorgis, Dimitrios I.. (2019). Process design and optimisation for the continuous manufacturing of Nevirapine, an Active Pharmaceutical Ingredient (API) for H.I.V. treatment. Organic Process Research & Development. 23. 10.1021/acs.oprd.8b00381.
12. Mohammed, Mohammed & Moles, Rebekah. (2016). The Impact of Pharmaceutical Care Interventions on Health-Related Quality-of-Life Outcomes:

A Systematic Review and Meta-analysis. Annals of Pharmacotherapy. 50. 10.1177/1060028016656016.

13. Oke, Emmanuel. (2022). The Right to Health in Pharmaceutical Patent Disputes (South Centre Research Paper No. 145).
14. Shamshina, Julia & Berton, Paula & Wang, Hui & Zhou, Xiaosi & Gurau, Gabriela & Rogers, Robin. (2018). Ionic Liquids in Pharmaceutical Industry. 10.1002/9781119288152.ch20.
15. Xiaoluan, Sun & Wei, Jing & Yao, Yuan & Chen, Qiutong & You, Daiting & Xu, Xinglu & Dai, Jing & Yao, Yanping & Sheng, Jingyi & Li, Xin. (2018). Availability, prices and affordability of essential medicines for children: A cross-sectional survey in Jiangsu Province, China. BMJ Open. 8. e023646. 10.1136/bmjopen-2018-023646