International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Formulation and Evaluation of Lamotrigine Spherules with Robust Gelation Technique

Sumedh Paralkar[1], Yogesh Thorat[2], Balkirshna Tiwari[3], Sweta Kota[4], Sneha Kota[5]

[1]Assistant. Professor, Department. of Pharmaceutics,Amepurva Fourm's Nirant Insitute of Pharmacy, Solapur, Maharashtra, India
[2]Associate. Professor, Department. of Pharmaceutics, D.S.T.S. Mandal's College of Pharmacy, Shivdare Campus, Shrikant Nagar, Jule Solapur-1, Vijapur Road, Solapur- 413004
[3]Vice Principal, Dept. of Medicinal Chemistry, Amepurva Fourm's Nirant Insitute of Pharmacy, Solapur, Maharashtra, India
[4,5]Amepurva Fourm's Nirant Insitute of Pharmacy, Solapur, Maharashtra, India

ABSTRACT:
Many freshly created high-potential medications have low water solubility, which is a challenge in formulation development. The study aimed to improve the solubility of Lamotrigine, a weakly soluble medication classified as BCS class II, by solid dispersion techniques. Lamotrigine solid dispersion was created using the solvent evaporation method, and the formulation was assessed using stability tests, Fourier transform infrared spectroscopy (FTIR), and physical properties. Preformulation investigations yielded satisfactory results, therefore pellets were formed and evaluated.[2] Solid dispersion had a different pharmacokinetic profile than pure medication, which could be attributable to Lamotrigine's faster dissolution rate from solid dispersion.[4]
Solid dispersions have sparked widespread interest as an effective technique of increasing the dissolution rate and thus bioavailability of a variety of weakly water-soluble medicines. Solid dispersions of weakly water-soluble medicines with water-soluble carriers have reduced the occurrence of these difficulties and increased solubility.[6]

INTRODUCTION:

Poorly water-soluble medications are becoming increasingly problematic in terms of achieving sufficient dissolving within the gastrointestinal tract, which is required for good bioavailability. It is the challenge of medicinal chemists to ensure that new medications are not only pharmacologically active but also have enough solubility to enable fast enough dissolution at the site of delivery, which is commonly the gastrointestinal system. It is estimated that 40% or more of new chemical entities (NCEs) being identified through combinatorial screening programs are poorly soluble in water, which is a critical determinant of oral bioavailability and solubility of many newly developed high-potential drugs is an obstacle in formulation development. Furthermore, the Biopharmaceutical Classification System (BCS) highlights dissolution as the rate-limiting step for oral absorption of class II and IV drugs
Solubilization techniques include the addition of a cosolvent, salt formation, prodrug design, complexation, particle size reduction, and the use of surface active agents, the use of solvate and

hydrates, polymorphs, hydrotrophy, the use of absorbents, pH adjustment, solubilizing vehicles, and so on. Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix during the solid stage to produce higher dissolution rate, sustained release of pharmaceuticals, altered solid state properties, and enhanced release of drugs. Traditionally, solid dispersions (SDs) were employed to increase the dissolving characteristics and bioavailability of weakly water-soluble medicines. Lamotrigine is an antiepileptic medication of BCS class II that creates significant solubility issues. To boost the solubility of the medicine, solid dispersion was used with two polymers HPMC, and the solid dispersion mixture was evaluated, and pellets were made after receiving satisfactory findings.
The orifice-ionic gelation technique using sodium alginate and calcium chloride was used to make lamotrigine pellets in this study. Pellets formulated with lamotrigine were tested for particle size, entrapment efficiency, in-vitro drug release, rheology study, and loose crystal surface. [2]

MATERIALS:

1. Lamotrigine drug
2. HPMC
3. Ethanol
4. Sodium alginate solution
5. Calcium chloride
6. Phosphate buffer [pH 6.8 , pH 7.4]
7. 0.1N HCL

METHODS:

- **Preparation of Solid Dispersion :**

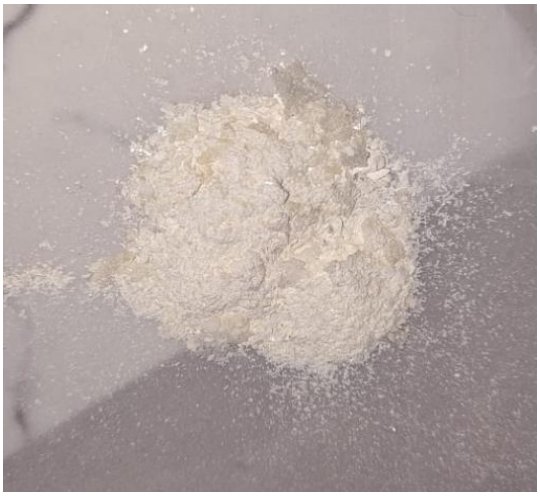

Fig 1: Lamotrigine Solid Dispersion

For the preparation of solid dispersion of Lamotrigine the method used is known as ‘solvent evaporation method’. In this method the required amount of lamotrigine drug is dissolved in required amount of solvent i.e.Ethanol along with polymer i.e.HPMC further the solvent was completely evaporated at 45 degree celcious with contineous stirring to obtain dry mass

- **Preparation of Pellets:**

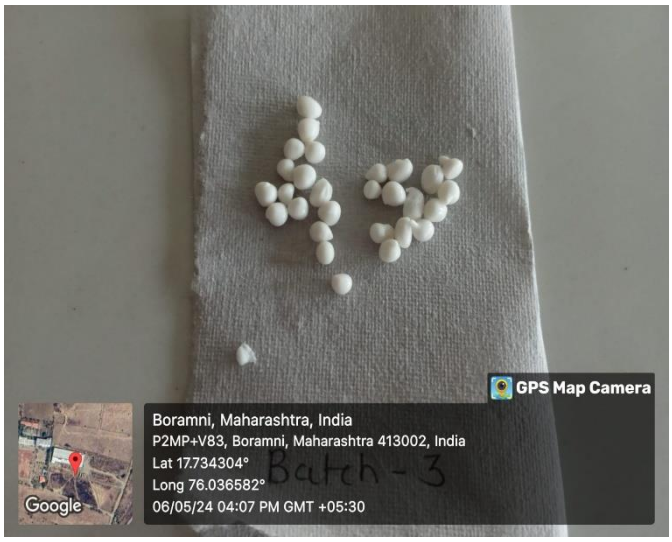

Fig 2:Pellets of Solid Dispersion

For the preparation of pellets of lamotrigine solid dispersion the method used is Orifice ionic gelation technique. In this method the sodium alginate solution was prepared in 50 ml of water and solid dispersion was added to the solution further separately prepare 10 % Calcium chloride solution . To this solution added dispersed solution drop by drop by contineous stirring at less than 300 rpm further they are dried for 2 days at room temperature in Desicator

EVALUATION OF THE LAMOTRIGINE SOLID DISPERSION:

1. **physical Appearance:**

Colour and appearance were assessed for the two batches of Lamotrigine solid dispersions.[2]

2. **Lamotrigine content determination:**

An accurately weighed amount of each preparation was dissolved in a small volume of methanol and then diluted further with methanol. The amount of lamotrigine was measured spectrophotometrically at 308 nm using Perkin Elmer UV-visible spectrophotometer[2]

3. **Stability studies**:

Stability tests were performed on pharmacological substances packaged in a container closure system that is identical to or resembles the packing intended for storage and distribution. Stability tests were conducted on both batches of solid dispersion by storing 1 gm of solid dispersions and excipients in an amber screw-capped bottle at room temperature for 4 weeks. After four weeks, the solid dispersions and excipients were visually inspected for any physical changes, and the drug content was estimated.[2]

4. **Infrared spectroscopy:**

The infrared spectra (IR) of Lamotrigine and solid dispersions were obtained using FTIR (Perkin Elmer 1600 Series). The KBr pellet method was used to collect the IR spectra.[2]

5. **Flow qualities**:

The flow properties of solid dispersion were investigated by finding Carr's index and angle of repose.[2]

CHARACTERISTICS OF PELLETS:

1. **Determination of Moisture Content**:

The Formulations were subjected to Moisture Content Study, by placing the Micropellets at 60°c for 3 hr in an Hot Air Oven[2]

2. Loose Surface Crystal Study (LSC):

This study was carried out to determine the amount of drug present on the surface of micropellets, which could be released immediately in the dissolving fluid. 100mg of micropellets (# 22 size) were suspended in 100ml of phosphate buffer (pH 6.8) to simulate the dissolving media. The materials were violently agitated in a mechanical shaker for 15 minutes. The amount of medication leached from the surface was measured spectrophotometrically at 308nm. The percentage of drug released in comparison to the amount of drug enclosed in the sample was recorded.[2]

3. Determination of Drug Entrapment Efficacy:

About 100mg of micropellets (# 22 sizes) were carefully weighed and dissolved in 25ml of phosphate buffer (pH 7.4) overnight, and an aliquot of the filtrate was spectrophotometrically analysed at 308 nm using Perkin Elmer after adequate dilution. The method's dependability was determined by doing a recovery analysis using a known dose of drug, with or without polymer. Recovery rates averaged 98.59 ± 0.50%. Each batch's drug concentration was measured in micropellets of different sizes, and the mean ± SD was calculated. The formula to calculate Drug Entrapment Efficiency (DEE) is as follows:[2]

$$\%DEE = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

4. Study of Invitro Dissolution:

To investigate drug release from the micropellets, the USP Dissolution device I (Electrolab) was utilised. For two batches, the dissolve conditions (100 mg pellets, 37± 2°C, 100 rpm, 1000 ml of USP pH 1.2, n = 3, coefficient of variation < 0.05) were kept constant. A 2 millilitre sample was taken out at predetermined intervals, and after a proper dilution, it was measured at 308 nanometers using a Perkin Elmer spectrophotometer.[2]

RESULTS:

EVALUATION OF THE LAMOTRIGINE SOLID DISPERSION:

1. Physical Appearance:

Fig 3:Lamotrigine Solid Dispersion

Using a solvent evaporation process, fine powder lamotrigine dispersions were created.

2. Finding the Uniform Lamotrigine Content:

It was discovered that the produced formulations' drug content uniformity was 96.54±2.31

3. Investigations on the stability of two batches of solid dispersions:

Fig 4: Stability studies of lamotrigine Solid dispersion

Stability studies were carried out by storing 1gm of solid dispersion And excipient (HPMC) in amber coloured bottles at room temperature for 4 weeks . These batches not showed any significant change

4. IR Spectroscopy:

TABLE 1: IR Interpretation of Lamotrigine Solid Dispersion

Reported Range Cm^{-1}	Observed Cm^{-1}	Functional Group
3490 - 3430	3451.37	Heterocyclic amine N-H Stretch
3360 - 3310	3329.84	Aliphatic Secondary Amine , >NH Stretch
3330 - 3250	3210.64	N-H Stretching Aliphatic Primary Amine
3000 - 2840	2923.61	C-H Stretching Alkane
2000 - 1660	1620.29	Aromatic Combination Bands
1560 - 1540	1556.36	Aliphatic Nitro Compound N-O Stretch
1555 - 1485	1492.01 1462.05	C=C-C , Stretch , Aromatic Ring
1385 - 1380	1384.16	C-H Bend Alkane Geminal dimethyl
1190 - 1130	1144.35	2^0 Amine , CN Stretch
1150 - 1085	1112.33	Aliphatic Ether Stretch
	1055.13	
1225 - 950	950	Aromatic C-H in Plane Bend
840 - 790	790	C=C Bend Alkene
850 - 550	717	C-Cl Stretch

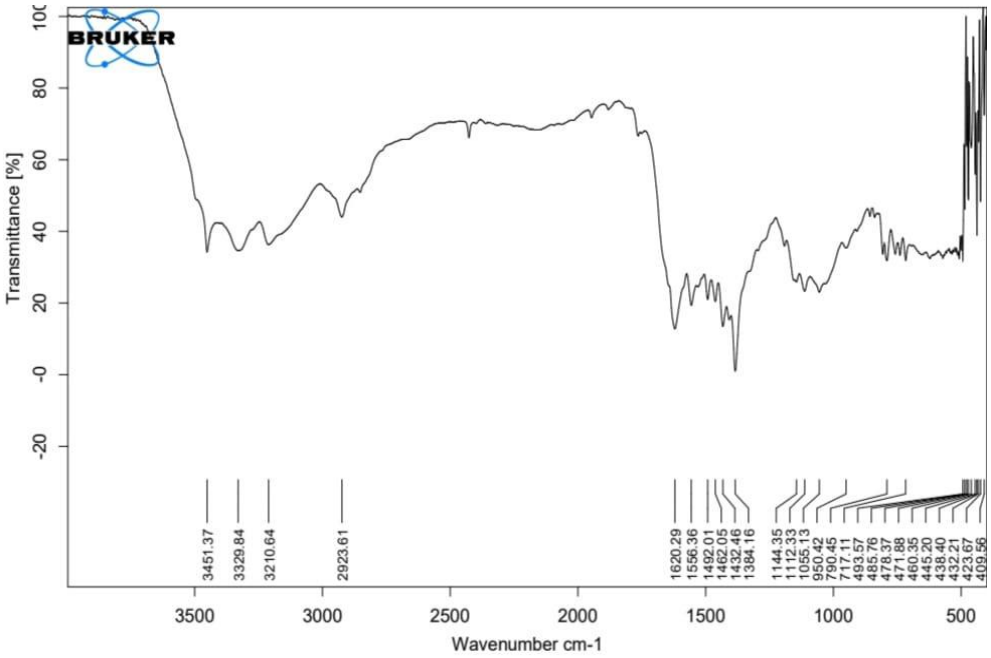

Fig 5: Spectra of Lamotrigine Solid Dispersion

5. Flow properties:

TABLE 2: Evaluation of Flow Properties of Lamotrigine Solid Dispersion

Bulk Density	Tapped Density	Compressibility Index (%)	Hausners Ratio	Angle of Repose ( )
0.2857	0.3333	14.28	1.16	26.56

Compressibility Index = Excellent , Hausners Ratio = Good , Angle of Repose = Good

14.28 is the solid dispersions' compressibility index value. This suggests that the powder blend has Excellent flow characteristics. The solid dispersions' angle of repose value of 26.56 were found to be Good in accordance with the flow chart. Because of the good flow feature, compressing the tablet would require less lubricant.

CHARACTERISTICS OF PELLETS:

1) Moisture Content:

The all-around efficiency of the optimised drying conditions is indicated by the low moisture content of the pellets. Better medication stability in the pellets is ensured by low moisture content.

TABLE 3: Evaluation of Moisture Content of Pellets

Batches	Moisture Content
Batch 1	1.42
Batch 2	1.40

2) Loose Surface Crystal:

One crucial factor that indicated how much medication was present on the pellet surface without adequate trapping was the loose surface crystal (LSC) investigation. Copolymer concentration increased, and LSC as a percentage declined dramatically

TABLE4: Loose Surface Crystal Study of Pellets

Batches	Loose Surface Crystal Study
Batch 1	3.64 ±0.2
Batch 2	3.60 ±0.23

3) Drug Entrapment Efficiency:

Table 5 demonstrates that both batches drug entrapment effectiveness was good.

TABLE 5: Evaluation of Drug Entrapment Efficiency of Pellets

Batches	Drug Entrapment Efficiency
Batch 1	97.52±0.30
Batch 2	97.45±0.25

4) In-Vitro Dissolution Study:

Drug release investigations were conducted in stomach fluid (SGF). Drug release profiles were given by charting the amount of Lamotrigine released over time. Table 6,7 and Figure 9,10 Respectively demonstrate the release test findings for alginate-based pellets. Lamotrigine was released rapidly, with over 90% release within 30 min.

TABLE 6: Dissolution Studies of Batch1 Pellets

Time (Hr)	Percentage Drug Release
0	0
5	16.20
10	28.30
15	44.06
20	62.66
30	93.89

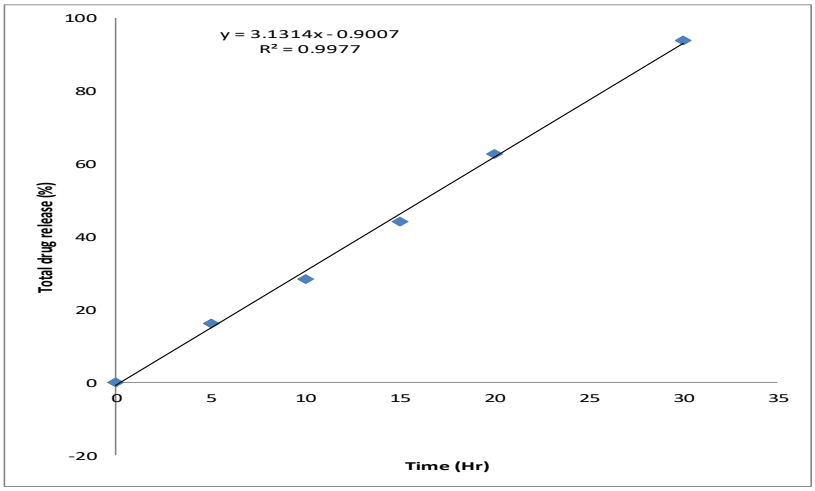

Fig 6: Release Profile of Batch

TABLE 7: Dissolution Studies of Batch2 Pellets

Time (Hr)	Percentage Drug Release
0	0
5	15.23
10	28.25
15	43.18
20	60.02
30	91.31

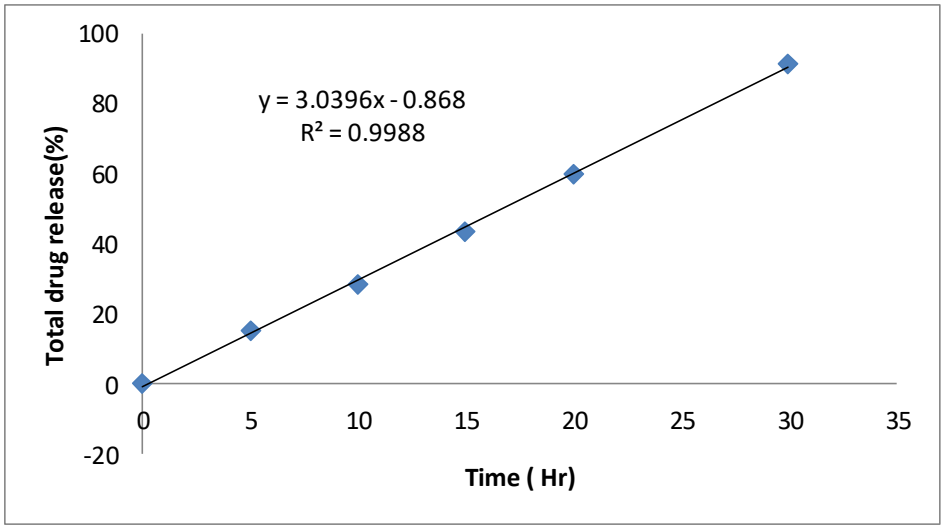

Fig 7: Release Profile of Batch 2

Conclusion:

Lamotrigine's solubility was found to be enhanced by the solid dispersion approach in vitro dissolution experiments, as well as by the combination of polymers. Solid dispersion has superior flow characteristics, making formulation simple. The medication and the excipient did not interact, according to the FTIR and stability experiments. The pellets were prepared using a straightforward, repeatable method called orifice ionotropic gelation, which yields beads with consistent sizes and shapes.

The prepared beads were distinct and spherical in shape. The produced beads had distinct shapes and were spherical in shape. Sodium alginate pellets demonstrated a good drug entrapment efficiency, suggesting that the drug was effectively entrapped. Moreover, the LSC data suggested that the drug was less surface-active.In vitro studies suggest that sodium alginate aids in drug release from pellets, with over 90% liberated after 30 minute

REFERENCES:

1. Shahinaze A. Fouad, Fady A. Malaak, Preparation of solid dispersion system for enhanced dissolution of poorly water soluble diacerein, Plose one 1-26
2. S. D. Bhoir and S. Agrawal, Pelletization of Lamotrigine Solid Dispersion for Improved Solubilization, International Journal of Pharmaceutical Sciences and Research, vol 2(9), 2380-2386
3. Lingam Praveenkumar, Ch. Saibabu, Formulation and Evaluation of Lamotrigine Solid Dispersion, International Journal of Reserch Publication and Reviews , ISSN 2582-7421

4. A. Mohan, M. Madhavi, G. Swetha, Preparation, In Vivo Characterization of Solid Dispersion of Lamotrigine Using Solvent Evaporation Technique, ISRO Journal of Pharmacy vol 5,Issue 1,PP 54-59
5. Pankaj p. Amrutkar, Sanjay B. Patil, Abhijeet N. Todarwal, Design and Evaluation of Taste Masked Chewable Dispersible Tablet of Lamotrigine by Melt Granulation, International Journal of Drug Delivery 2,(2010) 188-196
6. Sameer Singh, Raviraj Singh Baghel and Lalit Yedav, A review on Solid Dispersion, International journal of Pharmacy and Life Sciences, ISSN :0976-7126
7. Sanklecha VM, A Systemic Review on Solid Dispersion :Enhancing the Solubility Of Poorly Soluble Drug, Austin Journal of Nanomedicine and Nanotechnology, vol 8 Issue 1-2020, ISSN : 2381-8956
8. Ali Farmoudeh, Anahita Rezaeiroshan, Mohammadreza Abbaspour, Solid Dispersion Pellets :An Efficient Pharmaceutical Approach to Enrich the Solubility and Dissolution Rate of Deferasirox, Hindawi BioMed Research International, vol 2020,12 pages Article ID 8583540
9. Jatinderpal Singh ,Rajeev Garg,and Ghanshyam Das Gupta , Enhancement of Solubility of Lamotrigine by Solid Dispersion and Development of Orally Disintegrating Tablets Using 3 Full Factorial Design ,Hindawi Publishing Corporation Journal of Pharmaceutics ,vol 2015,Article ID 828453, 8 pages
10. Ramzi Shawahna, Hala Sabaaneh Amal Daraghmeh, Solubility of Lamotrigine in age-specific biorelevent media that stimulated the fasted - and fed -conditions of the gastric and intestinal environments in pediatrics and adults : implications for traditional, re-formulayed, modified, and new oral formulation, BMC biotechnology (2023) 23:36
11. Poluri koteswari, Suvarnala Sunium, Formulation Development and Evaluation of Fast Dusintegrating tablets of Lamotrigine using liquid-solid Technique, International Journal of pharmaceutical Investigation 2014, vol4, Issue 4,207-214
12. Vinay Sharma, Surya pratap Singh, Nitin Naman, Khinchi M. P, Formulation and Evaluation of Orally Disintegrating Tablet of Lamotrigine, Asian Journal of Pharmaceutical Research and Development, vol5 (2) 2017 : 1-10
13. Syed Sohali, Mahammad Rafi shaik, Formulation and invitro Characterization of Lamotrigine fast dissolving tablets by solid duspersion technique, International Journal of Pharmacy and Industrial Journal of Pharmacy and Industrial Research, vol 12,Issue 4 , 2023 ISSN : 2231-3656
14. Gopa Roy Biswas, Hydroxy Propyl Methyl Cellulose : Different Aspects in Drug Delivery, Article in Journal of pharmacy and pharmacology 2016 381-385
15. Saif Aldeen Jaber, Mohamed Saadh, The effect of polymeric films of hydroxypropyl methyl cellulose (HPMC) /Chitosan on olfoxacin release, diffusion, and biological activity, Polym Eng Sci. 2023 ; 63(9) :2871-2877
16. Pattaraporn Panraksa, Suruk Udomsom, Hydroxypropyl Methyl cellulose E15, Polymers 2020 , 12,2666 ;
17. Arno A. Enose, priya k. Dasan, Formulation and Characterization of Solid dispersion prepared by Hot Melt Mixing , Hindawi publishing Corporation Journal of Pharmaceutics, vol 2014 , 13 pages
18. Athira R. Nair, Yarlagadda Dani Lakshman , Overview of Extensively Employed polymeric carriers in Solid Duspersion Technology, AAPS Pharma Sci Tech (2020) 21: 309

19. Singh Jaskirat, Walia Manpreet, Solubility Enhancement By Solid dispersion Method, Journal of Drug Delivery and Therapeutics; 2013 , 3(5), 148-155
20. Bhumika kumar, Solid Dispersion -A Review, Pharma Tutor ; 2017 ; 5(2) ; 24-29
21. Shirke S. H, Shewale S. B, Kulkarni A. S, Solid Dispersion : A Novel Approach for Poorly Water Soluble Drugs, International Journal of Current Pharmaceutical Research, vol 7,Issue
5. 4,2015
22. Elder DP, Holm R, Kuentz M. Medicines for Pediatric Patients-Biopharma-ceutical, Developmental, and Regulatory Considerations. J Pharm Sci. 2017;106(4):950–60.
23. Del Moral Sanchez JM, Gonzalez-Alvarez I. Biopharmaceutical optimization in neglected diseases for paediatric patients by applying the provisional paediatric biopharmaceutical classification system. 2018, 84(10):2231–41.
24. Gandhi SV, Rodriguez W, Khan M, Polli JE. Considerations for a Pediatric Biopharmaceutics classification system (BCS): application to five drugs. AAPS PharmSciTech. 2014;15(3):601–11.
25. Batchelor HK, Kendall R, Desset-Brethes S, Alex R, Ernest TB. Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients. Eur J Pharm Biopharmaceu-tics: Official J Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2013;85(3 Pt B):833–42.
26. Dahan A, Wolk O, Kim YH, Ramachandran C, Crippen GM, Takagi T, Bermejo M, Amidon GL. Purely in silico BCS classification: Science based quality standards for the world's drugs. Mol Pharm. 2013;10(11):4378–90.
27. Wolk O, Agbaria R, Dahan A. Provisional in-silico biopharmaceutics classifica-tion (BCS) to guide oral drug product development. Drug Des Devel Ther. 2014;8:1563.
28. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hus-sain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP. Molecular proper-ties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm. 2004;1(1):85–96.
29. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of essential Medicines according to the biopharmaceutics classification system. Eur J Pharm Biopharmaceutics: Official J Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2004;58(2):265–78.
30. Shawahna R, Rahman N. Evaluation of the use of partition coefficients and molecular surface properties as predictors of drug absorption: a provisional biopharmaceutical classification of the list of national essential medicines of Pakistan. Daru: J Fac Pharm Tehran Univ Med Sci. 2011;19(2):83–99.
31. Charoo NA, Cristofoletti R, Dressman JB. Risk assessment for extending the Biopharmaceutics classification system-based biowaiver of immediate release dosage forms of fluconazole in adults to the paediatric population. J Pharm Pharmacol. 2015;67(8):1156–69.
32. Brigo F, Igwe SC, Lattanzi S. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Cochrane Database Syst Rev. 2019;2(2):Cd003032.
33. Brigo F, Jones K, Eltze C, Matricardi S. Anti-seizure medications for Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2021;4(4):Cd003277.
34. Besag FMC, Vasey MJ, Sharma AN, Lam ICH. Efficacy and safety of lamotrigine in the treatment of bipolar disorder across the lifespan: a systematic review. Ther Adv Psychopharmacol. 2021;11:20451253211045870.

35. Bendtsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, Eide PK, Leal PRL, Maarbjerg S, May A, et al. European Academy of Neurology guideline on trigeminal neuralgia. Eur J Neurol. 2019;26(6):831–49.
36. Caleffi-Marchesini ER, Borghi-Pangoni FB, Macente J, Chiamulera-Mantovani P, Mazucheli J, Cristofoletti R, Diniz A. Exploring in vitro solubility of lamotrigine in physiologically mimetic conditions to prospect the in vivo dissolution in pediatric population. Biopharm Drug Dispos. 2023;44(2):147–56.
37. Porat D, Azran C, Mualem Y, Vainer E, Gibori R, Vaynshtein J, Dukhno O, Dahan A. Lamotrigine therapy in patients after bariatric surgery: potentially ham-pered solubility and dissolution. Int J Pharm. 2022;612:121298.
38. Vaithianathan S, Raman S, Jiang W, Ting TY, Kane MA, Polli JE. Biopharmaceu-tic Risk Assessment of brand and generic lamotrigine tablets. Mol Pharm. 2015;12(7):2436–43.
6. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–20.
7. (EMA) EMA. : Committee for Medicinal Products for Human Use. Guideline on the investigation of bioequivalence. In.; 2010
39. (FDA) UFaDA. : Draft Guidance. Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. In: Food and Drug Administration, Rockville, MD 2015.
40. Kortejärvi H, Malkki J, Shawahna R, Scherrmann JM, Urtti A, Yliperttula M. Pharmacokinetic simulations to explore dissolution criteria of BCS I and III biowaivers with and without MDR-1 efflux transporter. Eur J Pharm Sciences: Official J Eur Federation Pharm Sci. 2014;61:18–26.
41. Kortejärvi H, Shawahna R, Koski A, Malkki J, Ojala K, Yliperttula M. Very rapid dissolution is not needed to guarantee bioequivalence for biopharmaceutics classification system (BCS) I drugs. J Pharm Sci. 2010;99(2):621–5.
42. Shawahna R. Pediatric Biopharmaceutical classification system: using age-appropriate initial gastric volume. AAPS J. 2016;18(3):728–36.
43. Polli JE. In vitro studies are sometimes better than conventional human phar-macokinetic in vivo studies in assessing bioequivalence of immediate-release solid oral dosage forms. AAPS J. 2008;10(2):289–99.
44. Abdel-Rahman SM, Amidon GL, Kaul A, Lukacova V, Vinks AA, Knipp GT. Sum-mary of the National Institute of Child Health and Human Development-best pharmaceuticals for Children Act Pediatric Formulation Initiatives Workshop-Pediatric Biopharmaceutics classification system Working Group. Clin Ther. 2012;34(11):11–24.
45. Batchelor H. Paediatric biopharmaceutics classification system: current status and future decisions. Int J Pharm. 2014;469(2):251–3.
46. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key consid-erations and current challenges. Adv Drug Deliv Rev. 2014;73:102–26.
47. Shawahna R, Zyoud A, Haj-Yahia A, Taya R. Evaluating solubility of Celecoxib in Age-Appropriate fasted- and Fed-State gastric and intestinal Biorelevant Media Representative of Adult and Pediatric Patients: implications on Future Pediatric Biopharmaceutical classification system. AAPS PharmSciTech. 2021;22(3):84.

48. Maharaj AR, Edginton AN, Fotaki N. Assessment of Age-Related changes in Pediatric Gastrointestinal solubility. Pharm Res. 2016;33(1):52–71.
49. Martir J, Flanagan T, Mann J, Fotaki N. BCS-based biowaivers: extension to paediatrics. Eur J Pharm Sciences: Official J Eur Federation Pharm Sci. 2020;155:105549.