The Bioscan AN INTERNATIONAL QUARTERLY JOURNAL OF LIFE SCIENCES 21(2): S.I (2), 158-175, 2026 www.thebioscan.com

Recent Advances in Novel Drug Delivery System for Antidepressants: Emphasis on Gastroretentive and Sustained-Release Technologies

Gaurang K Parmar*[1], Shubham Singh[1], Sanjesh Rathi[1]

1. School of Pharmacy, Rai University Ahmedabad, Gujarat, India.

*Corresponding Author: Gaurang K Parmar, School of Pharmacy, Rai University Ahmedabad, Gujarat, India, Mail Id : gkparmar29@gmail.com

DOI: https://doi.org/10.63001/tbs.2026.v21.i02.S.I(2).pp158-175

KEYWORDS
Depression,
Antidepressants,
Novel drug delivery systems,
Gastroretentive drug delivery system,
Floating drug delivery system.

Received on:
18-02-2026
Accepted on:
04-03-2026
Published on:
14-04-2026

Abstract

This review article looks at how depression lasts a long time, needing ongoing use of drugs such as amitriptyline, fluoxetine, sertraline, or duloxetine. Yet, their impact often falls short because they do not absorb well, break down too quickly in the liver, or people fail to take them regularly. New ways of giving medicine now help - by changing when and where the drug releases, keeping it longer in the stomach, and smoothing out levels in the blood. Focus lands on fresh advances: pills that float, stick to tissue, stay put in the gut, or drip-feed medication slowly. Methods used to build these forms come under scrutiny - the materials chosen, how the dose escapes into the body, what scientists are exploring next.

1. Introduction

Each year brings depression into the lives of roughly 300 million individuals across the planet, an often disabling condition affecting minds.[1] Tiredness, lack of drive, trouble sleeping, and overwhelming despair - these signs appear far too frequently in regular routines.[2] Back in 2023, data from the World Health Organization suggested that 3.8 percent of everyone on Earth deals with this state, with one out of every twenty grown-ups included. When split by gender, 4 percent of men face it, while 6 percent of women do - that gap shows females encounter it at a rate nearly half again higher.[3] For those past age sixty, numbers climb to 5.7 percent.[4] Across nations and regions, more than 280 million now live within its reach.

Something deep inside the body might shift when sadness takes hold over time. Family patterns show up in who struggles, hinting at inherited pieces tucked within DNA. Those with relatives who've felt low often carry subtle differences in their genes.[5] These small shifts can shape how the brain grows, works, listens to stress, or reacts to life's pressures. A change here or there in chemistry - molecules, signals, pathways - can tilt things off balance. Wiring in the mind adapts, sometimes too much, sometimes not enough. History repeats quietly through bloodlines, not always obvious but present. The way nerves fire, connect, rewire - it all matters more than we see.

When brain chemicals go off track, one result might be depression. Serotonin matters a lot - it handles mood, appetite, rest, and thinking skills.[6] Low amounts or weak activity in this chemical often show up alongside sadness, messed-up eating habits, and trouble sleeping. Instead of feeling driven, people might feel empty if dopamine gets out of sync - this substance ties into enjoyment, drive, and managing emotions. Problems here tend to strip away joy, slow down effort, and shake emotional balance, feeding deeper lows. On another note, how we handle stress, stay alert, or feel emotionally steady links back to norepinephrine. If it acts strangely - too much or too little - the mind may slide toward classic signs of depression.

One major piece of how depression works involves chemicals in the brain - like serotonin, dopamine, along those lines norepinephrine - that get out of sync. On top of that, life experiences and mental pressures play a strong role too. Stressful events, whether sudden or lasting a long time, tap into several pathways that lead to deeper sadness or make existing low moods worse. A person's stress response system may be triggered by significant bad life events, such as the death of a loved one or unemployment.[7] This results in elevated cortisol levels and prolonged stimulation of the hypothalamic-pituitary-adrenal axis, which hinders hippocampus neurogenesis and affects prefrontal cortex function. Many treatments for depression have been created, and the effectiveness of antidepressants has been assessed.

For example, some people respond well to tricyclic antidepressants, a traditional class of antidepressant treatment, although they are linked to cardiovascular and central nervous system toxicity.[8] According to recent studies, complexing these medications with β-cyclodextrin or its derivatives can greatly improve pharmacokinetics, lower systemic toxicity, increase solubility and stability, and lessen

adverse responses.[9] An intelligent transdermal drug delivery device based on thermosensitive hydrogel successfully regulated medication release dosage by electrothermal heating in a rat model of depression. This approach greatly increased the percutaneous permeability of selegiline by using a liposomal formulation, which led to noticeable reductions in depression symptoms. Additionally, it lessened hippocampus damage and decreased serum levels of pro-inflammatory cytokines.[10]

There are now defined guidelines for the usage of antidepressants as a result of extensive study on the biomechanisms causing depression. Modulating neurotransmission is the main pharmaceutical strategy used to treat depression.[11] Nevertheless, two-thirds of major depressive disorder patients do not improve with the first course of medication. Additionally, about 30% of patients experience treatment-resistant depression, a condition in which they do not react to at least two typical antidepressants at the recommended dose and for at least six weeks.[12]

2. Causes of Depression

A complex mix of genetic, biochemical, psychological, social, and environmental elements leads to the onset of mental disorders like depression, with a focus on the connection between genetic factors and the environment.[13] The severity and individual variability of depression are also significantly influenced by these factors.

2.1. Environmental Risk Factors

The neighborhood environment, life and academic stress [14,15], disability, lower life satisfaction, and medical comorbidities [16] are just a few of the many environmental factors that affect depression. Other environmental factors include disease or physiological factors like HIV, cancer, postpartum problems, altered gut microbiota, and others [17,18]. These two types of criteria have also been integrated into the research in recent years. For instance, a study found that genetic vulnerability and exposure to ambient air pollution both have an impact on anxiety and depression. The interaction effects of genetic variations and air pollution on the risk of anxiety and depression were then assessed by genome-wide by environment interaction studies (GWEISs).[19]

2.2. Hormonal Imbalance Factors

People with endocrine abnormalities and chronic systemic diseases have a markedly increased risk of developing depression, according to numerous clinical investigations. [20,21], emphasizing how biochemical imbalances play a critical role

in the pathophysiology of depression. According to a cross-sectional study, women who use hormonal contraceptives have a greater prevalence of depression, and this relationship is related to the kind of contraception and how long it is used.[22] Notably, stress has no correlation with any cortisol indicators, yet postpartum depression symptoms are strongly correlated with some cortisol measurements. Cortisol dysregulation may show distinct, even opposing, symptoms in anxiety and depression.[23]

A finding showed longer sleep ties to better thyroid hormone response in individuals without thyroid issues but who feel down now and then - here, the TSHI stood out as a key marker.[24] Mice exposed to follicle-stimulating hormone acted withdrawn; their brains showed swelling, faulty nerve connections, and imbalances between glutamate and GABA, hinting at how FSH might play a role when mood drops low.[25]

3. Need for novel drug delivery systems in antidepressant therapy

Due to variations in absorption and hepatic first pass metabolism, conventional oral antidepressants frequently result in inconsistent exposure, delayed clinical improvement, and dose-limiting side effects that lower long-term adherence. In certain populations, such as children and adolescents, where trial reporting and harm-benefit balance have been discussed, there are also significant safety and tolerability issues.[26]

Because the blood–brain barrier (BBB) limits CNS medication entrance and can actively efflux medicines, many treatments enter the brain inefficiently. As a result, higher systemic doses may be required, potentially exacerbating peripheral side effects.[27] In order to smooth plasma concentration variations, decrease dosage frequency, and maximize brain exposure while lowering overall dose, novel delivery strategies are investigated.

3.1 What novel systems try to achieve

Bypass or overcome the blood-brain barrier and enhance brain targeting: Intranasal techniques can take advantage of nose-to-brain pathways and prolong residence time in the nasal cavity; in preclinical research, an intranasal thermoresponsive hydrogel significantly increased hippocampal exposure and improved antidepressant-like effects compared to oral dosing.[28]

Prevent first pass metabolism and enhance adherence: Transdermal delivery can allow easier regimens and possibly higher compliance by offering continuous

medication input, more stable levels, and decreased first pass loss.[29]

Controlled/triggered release and tolerance optimization: Nanocarriers and other cutting-edge platforms are designed to safeguard drugs, regulate release, and minimize off-target exposure, but translation frequently encounters difficulties with scalable production, repeatability, and long-term safety assessment.[30]

4. Overview of Novel Drug Delivery System for Antidepressants

4.1 Gastroretentive Drug Delivery Systems (GRDDS)

Gastroretentive systems are designed to remain in the stomach for extended periods, ensuring controlled drug release at the absorption site.

Mechanisms:

- **Floating systems** (low-density tablets or capsules that float on gastric fluid)
- **Mucoadhesive systems** (adhere to gastric mucosa)
- **Swelling systems** (expand upon hydration)
- **High-density systems** (sink and resist gastric emptying)

Figuring out how the stomach is built and works helps explain why some medicines need to stay there longer. Three parts form the stomach: the fundus, body, and antrum. Near the top, the fundus and body hold food after swallowing. Downstream, the antrum mixes and breaks down what's been eaten. A gate called the pylorus sits between the stomach and the small intestine. It filters contents, blocking larger chunks from moving forward. This valve-like structure controls what leaves the stomach.[31]. Pacing just after the antrum, before reaching the duodenum, sits the pylorus - a tight ring of muscle shaping how material moves. It works like a filter, holding back larger chunks so only smaller bits slip through. This gatekeeper ensures what enters the small intestine meets a size limit. Not everything makes it past this checkpoint. Cyclical contractions of the gastric muscles empty the stomach of its contents. Therefore, the fate of oral drug delivery systems is greatly influenced by the gastric emptying time. In both fed and fasting states, the process of stomach emptying takes place. Nonetheless, the motility patterns of

the two states differ significantly.[32]

Advantages:

- Increased bioavailability; extended stomach stay; and decreased frequency of dosage
- Improved absorption of medications with limited absorption windows, such as amitriptyline

Examples:

- Floating tablets of amitriptyline HCl using HPMC K15M and sodium bicarbonate
- Mucoadhesive microspheres of *venlafaxine* and *duloxetine*
- Floating in-situ gels for fluoxetine hydrochloride[33]

4.2 Sustained-Release (SR) System

Medicine stays effective longer when it trickles out slowly, thanks to special coatings that control how fast it dissolves. A steady drip beats a sudden rush, keeping things balanced inside the body over many hours.

Among the methods are:

Coated pellets or multiparticulate systems;

Osmotic pumps;

Matrix tablets (using HPMC, ethylcellulose);

Nanoparticles and microspheres with controlled release

Examples of studies include:

• Sertraline SR matrix tablets with a 12-hour release using HPMC K100M.

• Venlafaxine mini-tablets with dual release for biphasic administration.[34]

4.3 Mucoadhesive Systems

- These adhere to the gastric mucosa, providing prolonged retention and local delivery.
  Polymers Used: Carbopol, chitosan, sodium alginate, HPMC, polycarbophil.
  Recent Example: Mucoadhesive microspheres of *duloxetine hydrochloride* showed improved gastric residence and bioavailability.
- Mucoadhesive systems work by adhering to a spot in the gastrointestinal tract to prolong residence time. Mucoadhesive drug delivery systems have the potential to extend the residence periods of nasal, ocular, buccal, and vaginal drug delivery systems, according to research that started in the field of ophthalmics.[35][36] Hydrophilic macromolecules with lots of

hydrogen bonding groups made up the first generation of mucoadhesive polymers.[37]

- The mucoadhesive surface is wet during the contact stage, making close contact with the mucous membrane. In order to strengthen and solidify the adhesive junction and provide a longer adhesion, physicochemical interactions take place during the consolidation stage.[38] Studies on swelling, bioadhesivity, and zeta potential were carried out after various polymers were synthesized. The existence of a link was verified by correlating the results. The initial driving force for bioadhesion is thought to be the zeta potential, which is followed by interpenetration and subsequent secondary bonding. The study also highlighted the significance of the polymer's degree of ionization.[39]

4.4 Floating Tablets (Effervescent & Non-Effervescent)

In order to keep the dosage form in the stomach and proximal small intestine for several hours while releasing medication in a regulated manner, floating tablets are gastroretentive oral systems that are made to remain buoyant in gastric fluid. As has been demonstrated for other systemically acting medications formulated in floating systems, this is especially appealing for antidepressants whose absorption is preferred in the upper gastrointestinal tract, that exhibit pH-dependent solubility, or for which smoother 12–24 hour plasma profiles are desired to reduce peak-related adverse effects and improve adherence during long-term therapy.[40]

Effervescent floating tablets combine organic acids and gas-generating substances like sodium bicarbonate in a hydrophilic polymer matrix. When the gel comes into contact with stomach fluid, carbon dioxide is created and trapped inside the hydrated gel, reducing density and allowing for quick floating while maintaining drug release.[41] Swellable, gel-forming polymers (such as HPMC, alginates, and chitosan) are used in non-effervescent floating tablets to achieve low density; hydration and matrix expansion alone sustain buoyancy and adjust release without producing gas.[42]

Optimized floating matrices can stay in the stomach for several hours and offer consistent, prolonged release, which translates into better bioavailability and less frequent dosage, according to experience with cardio- and gastro-active medications.[43]

Comparably, effervescent or non-effervescent floating tablet antidepressant formulations are being investigated as a possible oral platform to improve upper-GI exposure, stabilize steady-state levels, and possibly improve clinical outcomes within long-term antidepressant therapy.

5. Polymers and Excipients in Formulation

Commonly used polymers include:

- **Hydrophilic matrices:** HPMC (K15M, K100M), Carbopol 934P, Sodium alginate.
- **Mucoadhesive agents:** Chitosan, Polycarbophil.
- **Effervescent agents:** Sodium bicarbonate, Citric acid.
- **Swellable materials:** PEG, Guar gum.

Selection Criteria:

- Compatibility with drug
- Controlled swelling and gel strength
- Non-toxicity and stability

6. Evaluation Parameters for Gastroretentive and Sustained-Release Antidepressant Systems

For gastroretentive and sustained-release formulations of antidepressants (e.g., floating tablets, beads, mucoadhesive systems, rafts, 3D-printed cores), evaluation must confirm both robust pharmaceutical quality and meaningful modulation of exposure.

6.1 Pre-Compression and Tablet / Unit Properties

- **Flow and compressibility of blends or granules**

  When buoyancy and release depend on the distribution of polymers and gas producing agents, uniform die filling, predictable unit weight, and consistent matrix structure are crucial. These factors are ensured by angle of repose, bulk/tapped density, Carr's index, and Hausner ratio.
- **Post-compression characteristics**

  As noted in GRDF design overviews, hardness,

thickness/diameter, friability, weight fluctuation, and assay/content consistency confirm mechanical integrity (critical for extended stomach occupancy) and dosage accuracy.[44]

Particle size, size distribution, morphology (SEM), and entrapment efficiency are also measured for multiparticulates (beads, microspheres) in order to relate surface area and polymer coating to mucoadhesion and release.[45]

6.2 Gastroretentive Performance

6.2.1 Floating / Buoyancy Parameters

- **Floating lag time**

  Time needed to achieve buoyancy in simulated gastric fluid; a shorter lag denotes quick stomach placement of floating beads or effervescent antidepressant tablets.[46]

- **Total floating time / duration of buoyancy**

  The amount of time the unit stays afloat without sinking or dissolving should preferably match or surpass the goal release window (e.g., ≥8–12 h for once daily systems).[47]

- **Tablet density**

  Determine the density directly or indirectly (using mass and volume) to make sure it is either above or below the gastric fluid density (≈1 g/cm³) for high density systems or below it for floating systems.[48]

- **Swelling / expansion index**

  The diameter/weight gain over time for non-effervescent or combination swellable-effervescent matrices reveals the strength of the gel layer and is correlated with diffusion path length and floating behavior.[47]

6.2.2 Mucoadhesive / Bioadhesive Measures

For mucoadhesive gastroretentive antidepressant systems:

- **Mucoadhesive strength / detachment force**

  Measured ex vivo (e.g., texture analyzer using gastric mucosa) as the force to separate the dosage form, indicating adhesion robustness.[49]

- **In vitro / ex vivo residence time**

  Duration of adhesion to mucosa in flowing or agitated media; longer times suggest improved gastric retention.[45]

6.3 In-Vitro Drug Release and Kinetic Modeling

- **Dissolution testing**
  carried out in simulated gastric juice or 0.1 N HCl, occasionally with a pH shift to replicate onward passage. Like other controlled GRDDS, profiles for antidepressants should show a steady, prolonged release with minimal burst.(50)
- **Kinetic models**
  Release data fitted to:
  - Zero-order (constant rate)
  - First-order (concentration-dependent)
  - Higuchi (diffusion from matrix)
  - Korsmeyer–Peppas (mechanism classification via release exponent)
    Many floating and mucoadhesive systems show non-Fickian/anomalous transport due to combined diffusion and erosion.[51]
- **Profile comparison (f2 factor)**
  Similarity factor f2*f*2 is applied when comparing new GR–SR antidepressant forms with theoretical or marketed profiles, as done for optimized gastroretentive tablets.[50]

6.4 Advanced Formulation-Specific Characterization

Depending on the technology:

- **Floating beads / rafts**
  Entrapment efficiency, yield, neutralization time and raft strength (for raft systems), and the influence of polymers on loading, buoyancy, and release.[46][52]
- **3D-printed gastroretentive shells**
  Dimensional accuracy, shell/wall thickness, infill percentage, and composition are linked to floating behavior and pulsatile or delayed release lag time.[53]
- **Solid-state and compatibility studies**
  FTIR, DSC, TGA, and XRD confirm absence of major drug–polymer interactions, physical stability, and maintenance of desired solid form within complex GRDDS.[52]

6.5 Stability Studies

- **Accelerated and long-term stability**
  Storage under ICH conditions (e.g., 25 °C/60% RH; 40 °C/75% RH) with periodic assessment of:
  - Appearance and mechanical integrity

- Assay and related substances
- Floating lag time and duration
- Mucoadhesive strength (if relevant)
- Dissolution profile and f2*f*2 vs. initial profile Stable mucoadhesive gastroretentive tablets have shown minimal change in these attributes over several months.[49]

6.6 In-Vivo / In-Situ Evaluation

6.6.1 In-Vivo Gastroretention

- **Imaging of gastric residence**
  X-ray with radiopaque markers (e.g., barium sulfate), gamma-scintigraphy, or fluoroscopy to visualize localization and retention time in stomach; these methods confirm the in vitro buoyancy and mucoadhesion data.[52]
- **Mean residence time (MRT) in stomach**
  Derived from imaging sequences to quantify how long the unit remains gastric; optimized swellable floating tablets can achieve MRT >5 h in human volunteers.[54]

6.6.2 Pharmacokinetics

- **Systemic exposure metrics**
  Cmax, Tmax, AUC, half-life, fluctuation index, and relative bioavailability in comparison to traditional extended-release or immediate-release antidepressants. The potential of GRDDS to improve oral bioavailability is demonstrated by the enhanced AUC and moderated Cmax observed in floating or raft-forming systems for various medications.[53]
- **Food effect and prandial state**
  Since retention is sensitive to fed/fasted conditions, evaluation under both states is recommended to better predict clinical performance.[54]

6.6.3 Pharmacodynamics / Behavioral Assessment

For antidepressant candidates:

- **Behavioral models**
  Similar to how analgesic results were associated with floating systems, prolonged or pulsatile exposure from gastroretentive matrices can be correlated with antidepressant-like effects in animals using forced swim tests, tail suspension tests, and chronic moderate stress paradigms.[53]

6.7 Translational and System-Level Evaluation

Finally, for "recent advances" that combine gastroretention with sustained-release (e.g., expandable, superporous, magnetic, or 3D-printed personalized systems), reviews emphasize:

- Integration of **predictive in vitro tests** mimicking gastric hydrodynamics, pH, and mechanical stress.
- Use of **physiologically relevant in vivo models** and human data to bridge lab performance with clinical reality.[54][55]

When combined, these assessment criteria offer a methodical framework for determining if a novel gastroretentive sustained release antidepressant delivery system is physiologically sound, pharmaceutically sound, and able to produce the desired therapeutic exposure profile.

7. Challenges and Future Perspectives

Despite progress, several issues persist:

- Variability in gastric emptying time affects GRDDS performance.
- Reproducibility of floating behavior in humans remains challenging.
- Scaling up effervescent systems requires control of humidity and CO_2 loss.
- Integration of **nanotechnology with GRDDS** (e.g., floating nanoparticles) is a promising next step.

Future Trends:

- Use of 3D printing to design customizable gastroretentive forms.
- Smart polymers responsive to pH or gastric motility.
- Hybrid systems combining floating + mucoadhesive mechanisms.

8. Conclusion

The oral administration of antidepressant medications has been transformed by innovative gastroretentive and sustained-release devices. These methods increase bioavailability, lower dosage frequency, and boost patient compliance by prolonging gastric residence time and preserving therapeutic plasma levels. The most promising methods are mucoadhesive systems, polymeric nanoparticles, and floating tablets based on HPMC. Next-generation antidepressant delivery systems with better treatment results

will be made possible by ongoing developments in polymer science, 3D printing, and nanotechnology.

References

1. Pu D, Luo J, Wang Y, Ju B, Lv X, Fan P, He L. Prevalence of depression and anxiety in rheumatoid arthritis patients and their associations with serum vitamin D level. Clinical rheumatology. 2018 Jan;37(1):179-84.
2. Rakel RE. Depression. *Prim Care*. 1999;26(2):211–224.
3. Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, De Girolamo G, De Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN. Cross-national epidemiology of DSM-IV major depressive episode. BMC medicine. 2011 Jul 26;9(1):90.
4. Reed PG, Boyd M, Buckwalter KC. Mental health of older adults. Western journal of nursing research. 1989 Apr;11(2):143-63.
5. Tabrizi F, Rosén J, Grönvall H, William-Olsson VR, Arner E, Magnusson PK, Palm C, Larsson H, Viktorin A, Bernhardsson J, Björkdahl J. Heritability and polygenic load for comorbid anxiety and depression. Translational Psychiatry. 2025 Mar 27;15(1):98.
6. Kanova M, Kohout P. Serotonin—Its synthesis and roles in the healthy and the critically ill. International journal of molecular sciences. 2021 May 3;22(9):4837.
7. Grossi G, Åhs A, Lundberg U. Psychological correlates of salivary cortisol secretion among unemployed men and women. Integrative Physiological and Behavioral Science. 1998 Jul;33(3):249-63.
8. Preskorn SH, Fast GA. Therapeutic drug monitoring for antidepressants: efficacy, safety, and cost effectiveness. The Journal of clinical psychiatry. 1991 Jun 1;52:23-33.
9. Văruț RM, Popescu AI, Gaman S, Niculescu CE, Niculescu AȘ, Dop D, Stepan MD, Ionovici N, Singer CE, Popescu C. Cyclodextrin-Based Drug Delivery Systems for Depression: Improving Antidepressant Bioavailability and Targeted Central Nervous System Delivery. Pharmaceutics. 2025 Mar 10;17(3):355.
10. Liu S, Huang S, Liu K, Han Y, Xiong F. The novel design of an

intelligent anti-depression transdermal drug delivery system. Biomaterials. 2023 Dec 1;303:122362.

11. Puryear CB, Brooks J, Tan L, Smith K, Li Y, Cunningham J, Todtenkopf MS, Dean RL, Sanchez C. Opioid receptor modulation of neural circuits in depression: What can be learned from preclinical data?. Neuroscience & Biobehavioral Reviews. 2020 Jan 1;108:658-78.
12. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008 Oct 16;455(7215):894-902.
13. Penner-Goeke S, Binder EB. Epigenetics and depression. *Dialogues Clin Neurosci*. 2019;21(4):397–405.
14. Rajbhandari P, Shrestha D. Prevalence and associated risk factors of tooth wear. J. Nepal Med. Assoc. 2018;56:719-23.
15. Quinn ME, Stanton CH, Slavich GM, Joormann J. Executive control, cytokine reactivity to social stress, and depressive symptoms: testing the social signal transduction theory of depression. Stress. 2020 Jan 2;23(1):60-8.
16. Subramaniam M, Abdin E, Sambasivam R, Vaingankar JA, Picco L, Pang S, Seow E, Chua BY, Magadi H, Mahendran R, Chong SA. Prevalence of depression among older adults-results from the well-being of the Singapore elderly study. Ann Acad Med Singapore. 2016 Apr 1;45(4):123-33.
17. Patten SB. Current perspectives on co-morbid depression and multiple sclerosis. Expert Review of Neurotherapeutics. 2020 Aug 2;20(8):867-74.
18. Kim BS, Chung PW, Kim BK, Lee MJ, Park JW, Chu MK, Ahn JY, Bae DW, Song TJ, Sohn JH, Oh K. The impact of remission and coexisting migraine on anxiety and depression in cluster headache. The journal of headache and pain. 2020 Dec;21(1):58.
19. Zhao M, Chen L, Yang J, Han D, Fang D, Qiu X, Yang X, Qiao Z, Ma J, Wang L, Jiang S. BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. Journal of affective disorders. 2018 Feb 1;227:226-35.
20. Gold PW, Chrousos GP. The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. Proceedings of the

Association of American Physicians. 1999 Jan;111(1):22-34.

21. Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Molecular psychiatry. 2002 Feb;7(2):140-56.
22. Yusuf AM, Warsame MO, Gedi S, Abdullahi NA, Ahmed DI. Prevalence of depression among women using hormonal contraceptives in Mogadishu, Somalia: a cross-sectional study. Open Access Journal of Contraception. 2024 Dec 31:89-98.
23. Weiss SJ, Xu L. Postpartum symptoms of anxiety, depression and stress: differential relationships to women's cortisol profiles. Archives of Women's Mental Health. 2024 Jun;27(3):435-45.
24. Xiao XQ, Fu FS, Xiang C, Yan HC. Sensitivity to thyroid hormones is associated with sleep duration in the euthyroid population with depression degree lower than moderate. Scientific Reports. 2024 Mar 19;14(1):6583.
25. Huang L, Sun S, Jiang G, Xie G, Yang Y, Chen S, Luo J, Lv C, Li X, Liao J, Wang Z. Follicle-stimulating hormone induces depression-like phenotype by affecting synaptic function. Frontiers in Molecular Neuroscience. 2024 Oct 21;17:1459858.
26. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. Bmj. 2004 Apr 8;328(7444):879-83.
27. Alyautdin R, Khalin I, Nafeeza MI, Haron MH, Kuznetsov D. Nanoscale drug delivery systems and the blood–brain barrier. International journal of nanomedicine. 2014 Feb 7:795-811.
28. Wang QS, Li K, Gao LN, Zhang Y, Lin KM, Cui YL. Intranasal delivery of berberine via in situ thermoresponsive hydrogels with non-invasive therapy exhibits better antidepressant-like effects. Biomaterials science. 2020;8(10):2853-65.
29. Brown L, Langer R. Transdermal delivery of drugs. *Annu Rev Med*. 1988;39:221–229.
30. Bhatia SN, Chen X, Dobrovolskaia MA, Lammers T. Cancer nanomedicine. Nature Reviews Cancer. 2022 Oct;22(10):550-6.
31. Talukder R, Fassihi R. Gastroretentive delivery systems: A

mini review. Drug development and industrial pharmacy. 2004 Jan 1;30(10):1019-28.

32. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. European Journal of Pharmaceutics and Biopharmaceutics. 2008 May 1;69(1):255-63.
33. Vaithilingam V, Dhamotharaswamy K. A Review on Novel Approach of Oral Drug Administration: Gastro Retentive Drug Delivery System. Indian Journal of Pharmaceutical Sciences. 2023 Jul 1;85(4).
34. Verma R. A Comprehensive Review on the Formulation and Evaluation of Sustained Release Drug Delivery System.
35. Bernkop-Schnürch A. Mucoadhesive systems in oral drug delivery. Drug discovery today: Technologies. 2005 Mar 1;2(1):83-7.
36. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of controlled release. 2006 Mar 10;111(1-2):1-8.
37. Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and in vitro characterization. Journal of controlled release. 2005 Oct 3;107(2):300-9.
38. Tur KM, Ch'ng HS. Evaluation of possible mechanism (s) of bioadhesion. International journal of pharmaceutics. 1998 Jan 12;160(1):61-74.
39. Thongborisute J, Takeuchi H. Evaluation of mucoadhesiveness of polymers by BIACORE method and mucin-particle method. International journal of pharmaceutics. 2008 Apr 16;354(1-2):204-9.
40. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug delivery. 2011 Feb 1;18(2):97-110.
41. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert opinion on drug delivery. 2006 Mar 1;3(2):217-33.

42. Adibkia K, Hamedeyazdan S, Javadzadeh Y. Drug release kinetics and physicochemical characteristics of floating drug delivery systems. Expert opinion on drug delivery. 2011 Jul 1;8(7):891-903.
43. Pahwa R, Saini N, Kumar V, Kohli K. Chitosan-based gastroretentive floating drug delivery technology: an updated review. Expert opinion on drug delivery. 2012 May 1;9(5):525-39.
44. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug delivery. 2011 Feb 1;18(2):97-110.
45. Md S, Ahuja A, Khar RK, Baboota S, Chuttani K, Mishra AK, Ali J. Gastroretentive drug delivery system of acyclovir-loaded alginate mucoadhesive microspheres: formulation and evaluation. Drug Delivery. 2011 May 1;18(4):255-64.
46. Radwan MA, Abou el Ela AE, Hassan MA, El-Maraghy DA. Pharmacokinetics and analgesic effect of ketorolac floating delivery system. Drug delivery. 2015 Apr 3;22(3):320-7.
47. Arza RA, Gonugunta CS, Veerareddy PR. Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPs PharmsciTech. 2009 Mar;10(1):220-6.
48. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. Pharmaceutics. 2019 Apr 20;11(4):193.
49. Patil S, Talele GS. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. Drug delivery. 2015 Apr 3;22(3):312-9.
50. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. Aaps PharmSciTech. 2004 Jun;5(2):34.
51. Adibkia K, Hamedeyazdan S, Javadzadeh Y. Drug release kinetics and physicochemical characteristics of floating drug delivery systems. Expert opinion on drug delivery. 2011 Jul 1;8(7):891-903.
52. Hanif M, Shah S, Rasul A, Abbas G, Zaman M, Amjad MW, Abdul Ghafoor Raja M, Khan HU, Ashfaq M, Iqbal O. Enhancement of oral

bioavailability of ibandronate through gastroretentive raft forming drug delivery system: in vitro and in vivo evaluation. International Journal of Nanomedicine. 2020 Jul 8:4847-58.

53. Reddy Dumpa N, Bandari S, A. Repka M. Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing. Pharmaceutics. 2020 Jan 8;12(1):52.
54. Schneider F, Koziolek M, Weitschies W. In vitro and in vivo test methods for the evaluation of gastroretentive dosage forms. Pharmaceutics. 2019 Aug 16;11(8):416.
55. Vrettos NN, Roberts CJ, Zhu Z. Gastroretentive technologies in tandem with controlled-release strategies: A potent answer to oral drug bioavailability and patient compliance implications. Pharmaceutics. 2021 Sep 30;13(10):1591.