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Assessment of Metformin Floating Tablets: Natural-Synthetic Polymer Combinations as Excipients for Enhanced Formulation

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ABSTRACT

This study focuses on optimizing a gastric floating tablet formulation designed specifically for Metformin HCl to improve the management of type 2 Diabetes Mellitus (DM). The formulation strategy combines natural and synthetic polymers, for a sustained-release (SR) prepared using wet granulation. The tablet contains Metformin HCl and a synergistic blend of sodium alginate and synthetic polymer (HPMC K4M). Methodological preparations involved rigorous evaluations to ensure adherence to required parameters. Results indicated that a batch with an HPMC K4M to sodium alginate (M7) ratio of 3:1 demonstrated optimal performance. Key findings included significant drug release, with over 90% of Metformin liberated within 8 hours in vitro, a swelling index exceeding 100% within 5 hours, and sustained buoyancy in simulated gastric fluid for over 10 hours. The integration of synthetic polymer enhances cost-effectiveness and reproducibility, while the natural polymer ensures biodegradability and reduces toxicity concerns. This optimized formulation of the Metformin floating tablet shows promise for further analysis and potential commercialization. Its attributes represent an advancement in type 2 DM management, providing favorable drug release kinetics and gastric buoyancy. Thus, it introduces a novel therapeutic approach to diabetes care.

Keywords: Metformin HCl, Gastric floating tablet, Diabetes Mellitus, Blend of Natural and synthetic polymers, Drug release kinetics

INTRODUCTION

The quest for sustained drug delivery systems propels the production of floating tablets, aiming to release contents consistently over an extended period while minimizing side effects (Kumari, 2018). Matrix dosage forms, especially oral sustained drugs, manipulate polymer swelling and release mechanisms to achieve controlled drug release, thereby enhancing drug function, reducing dosing frequency, minimizing dose release fluctuations, improving drug utilization, and reducing adverse effects. Advantages of sustained-release matrix drug delivery systems include enhanced patient comfort, reduced concentration fluctuations, improved drug absorption, enhanced drug potency, and cost-effectiveness, although challenges such as dose dumping and first-pass metabolism persist (Prakhar & Semimul, 2018).

Polymers, both synthetic and natural, play a crucial role in novel drug delivery systems, contributing to drug release mechanisms such as diffusion, degradation, and swelling. Gastroretentive delivery forms, including floating systems, emerge to overcome limitations of conventional oral dosage forms, offering enhanced compliance and effective drug concentration control (Bhatia & Bhatia, 2016). However, challenges like layer separation and compression resistance necessitate careful consideration in the formulation. Amid the global impact of

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diabetes mellitus, innovative treatment approaches are gaining significance, particularly in managing Type II diabetes characterized by insulin resistance and/or secretion challenges (Tan et al., 2019).

In diabetes treatment, the integration of natural and synthetic polymers in the formulation of floating tablets addresses complexities associated with insulin deficiency or resistance, enhancing treatment effectiveness and patient adherence (Meneguin et al., 2021). Various studies have contributed significantly to advancing drug delivery systems, highlighting the importance of tailored drug delivery systems across diverse therapeutic areas (Crommelin & Florence, 2013). In this context, various studies focus on optimizing, formulating, and analyzing gastric buoyant floating tablets specifically for Metformin HCl, aiming to revolutionize diabetes management (Huh et al., 2021; Nayak et al., 2011).

In this study, we are formulating Metformin HCl as a sustained-release layer utilizing a matrix mixture of synthetic and natural polymers. This formulation aims to reduce the frequency of administration, thereby improving patient compliance and offering a convenient medication option. Through this innovative experiment, we aspire to introduce a gastric buoyant floating tablet that effectively addresses the complexities of Type II diabetes while aligning with economic considerations and patient-centric convenience, marking a significant advancement in diabetes management.

MATERIALS AND METHODS

Materials

Metformin hydrochloride (Gift sample from Bafna Pharmaceuticals, Chennai), HPMC K4M (Synthetic polymer), Carbopol, PVPk30 and Sodium alginate (Natural polymer), Talc (Sisco Research Laboratories, Maharashtra), Sodium Bicarbonate, Citric acid (Loba Chemie PVT Ltd, Mumbai).

Drug- Excipient compatibility studies by Fourier transform infrared (FTIR) spectroscopy

Metformin, Sodium alginate, HPMC, and Carbopol were prepared for FT-IR analysis through individual grinding with KBr and subsequent combination. Following this preparation, the FT-IR instrument was calibrated, and the samples were placed on the holder for precise analysis. The acquired spectra were obtained within the wavelength range of 4000 to 400 cm^{-1} (D'Souza et al., 2008).

Formulation of metformin HCl SR granules

Metformin HCl sustained-release (SR) granules were prepared using the wet granulation method, which involved several sequential steps. Initially, polymers were accurately weighed, size-reduced, and thoroughly mixed as per Table 1. Subsequently, metformin, along with other specified ingredients in Table 1, was added to the polymer mixture, followed by passing through an 18-mesh screen to ensure proper blending. The resulting mixture underwent granulation using PVPK30 in isopropyl alcohol as a binder and was then screened through a #20-mesh size. After granulation, the mixture was dried at 60°C for 2 hours, screened through #18 mesh sizes, and supplemented with talc and magnesium stearate before tablet formulation (Diwedi et al., 2012; Hansuld & Briens, 2014).

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Table 1: Formulation of Metformin HCl granules

S/n	Ingredients	M1 mg	M2 mg	M3 mg	M4 mg	M5 mg	M6 mg	M7 mg	M8 mg	M9 mg
1	Metformin HCl	500	500	500	500	500	500	500	500	500
2	HPMC K4M	150	100	50	75	125	25	150	100	50
3	Sodium alginate	50	100	150	125	75	175	50	100	150
4	Carbopol	-	-	-	50	50	50	50	50	50
5	PVPk30	25	25	25	25	25	25	25	25	25
6	Sodium bicarbonate	50	50	50	50	50	50	50	50	50
7	Citric acid	15	15	15	15	15	15	15	15	15
8	MCC	52	52	52	02	02	02	02	02	02
9	Mg. stearate	5	5	5	5	5	5	5	5	5
10	Talc	3	3	3	3	3	3	3	3	3
11	Total	850	850	850	850	850	850	850	850	850

Assessment of Granule Properties

Angle of repose

The experiment commenced by setting up a fixed funnel over a burette stand at a 10cm height, with 20g of granules used. The granules were then allowed to flow freely through the funnel onto a sheet of graph paper placed underneath for measurement. After settling, precise measurements of the pile's height and radius were taken. The angle of repose (θ) was subsequently calculated using the arctangent function of the ratio of height (h) to radius (r), expressed as $\theta = \tan^{-1}(h/r)$ (Al-Hashemi & Al-Amoudi, 2018).

Bulk Density and Tapped Density

An empty graduated cylinder was weighed. A 20g quantity of the granules was then added to the cylinder, and the initial volume of the powder was recorded. Subsequently, the cylinder was tapped 300 times. Following tapping, the volume of the powder was measured once more. Bulk density was computed by dividing the mass of the powder by its initial volume, whereas tapped density was determined by dividing the mass of the powder by its tapped volume. The percentage compressibility and Hausner ratio were then calculated to evaluate the flow properties of the powder (Akseli et al., 2019).

Compressibility Index and Hausner's Ratio

The compressibility index, or Carr's index, reflects a powder's ability to be compacted, determined by the formula: Compressibility Index = (Tapped density - Bulk density) / Tapped density * 100. Additionally, Hausner's Ratio, indicating the relationship between tapped density and bulk density, is a critical parameter in pharmaceutical formulation. Mathematically, it's expressed as Hausner's Ratio = Tapped Density / Bulk Density.

Formulation of Metformin HCl tablets

The tablets, each totaling 850mg, were formed from previously prepared batches of granules M1 to M9 using a Rimek Mini Press-I tableting machine, a process that involved several steps. Initially, the machine was set up and calibrated according to the specifications of the tablets to be produced, and then the granules from batches M1 to M9 were carefully loaded into the hopper. Subsequently, the machine compressed the granules using punches and dies to form tablets of the desired size and shape, subjecting them to controlled pressure to

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ensure uniformity and consistency in tablet weight and hardness (Srivastava et al., 2005).

Evaluation of the Metformin HCl floating Tablets

Weight variation

From each formulation batch, 20 tablets were selected, and the average weights of those tablets were taken (Zaid et al., 2013).

Hardness

Six tablets were utilized to assess their hardness using the Monsanto device. The tablets were inserted into the device, crushed, and readings were taken to determine their hardness (Seitz & Flessland, 1965).

Friability

Ten tablets were employed and rotated for 4 minutes at 25 rpm using a Friabilator (Roche). The weight reduction indicated the friability value, which is expressed in percent. The official range is between 0.1% and 0.9% (Osei-Yeboah & Sun, 2015).

Floating Lag Time

A tablet was dropped into 100 mL of 0.1 N HCl, and the time it took for the tablet to move up to the surface was recorded. This process allowed for the assessment of the floating lag time, providing valuable information about the tablet's behavior in gastric fluid and its potential for prolonged gastric residence.

Total Buoyancy Time

The total floating time of the tablet that remained on the surface of a liquid was recorded.

Swelling Index

Swelling of tablet polymer entails absorption of a fluid which causes increases in weight and volume. It is expressed in percentage gain. A tablet was dropped inside 200ml of distilled water in a beaker and subsequent weight increase was weighed every hour for 5 hours.

Swelling index (S.I.) was calculated using the formula: $S.I = \left(\frac{Wt-Wo}{Wo}\right) x\, 100$, where Wt represents the weight of the tablet at time t, Wo denotes the initial weight of the tablet (Patil et al., 2011).

Drug content analysis

A stock solution of pure metformin HCl dissolved in water was prepared and diluted to create standard solutions covering the expected concentration range. Following this, twenty metformin floating tablets were crushed into a fine powder, dissolved in water, and subjected to UV spectrophotometric analysis at 232nm wavelength to construct a calibration curve and then correlating absorbance with standard solution concentrations for determining the concentration of the sample solution (Chen et al., 2001).

Dissolution test

The in-vitro dissolution study of the Floating Metformin HCl SR tablet was conducted using the USP apparatus II, also known as the Basket type. The parameters were set as follows: Dissolution Medium: 0.1N HCl, Temperature: 37°C, Volume: 900 ml, rotation per minute (rpm): 50, and UV Absorbance wavelength: 232 nm. Initially, the tablet was carefully placed in the dissolution medium, which was maintained at a temperature of 37°C. Subsequently, the basket apparatus was set into motion, rotating at 50 rpm to ensure thorough mixing of the dissolution medium. Throughout the dissolution process, UV absorbance at 232 nm was continuously monitored to assess the tablet's dissolution profile (Ilyés et al., 2019).

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RESULTS AND DISCUSSION

Incompatibility studies using FTIR analysis

FT-IR spectra of Metformin HCl and Glimepiride were acquired individually, followed by obtaining spectra of all excipients, including HPMC K4M, sodium alginate, and carbopol, and recording the spectra of the mixture comprising the drugs and excipients.

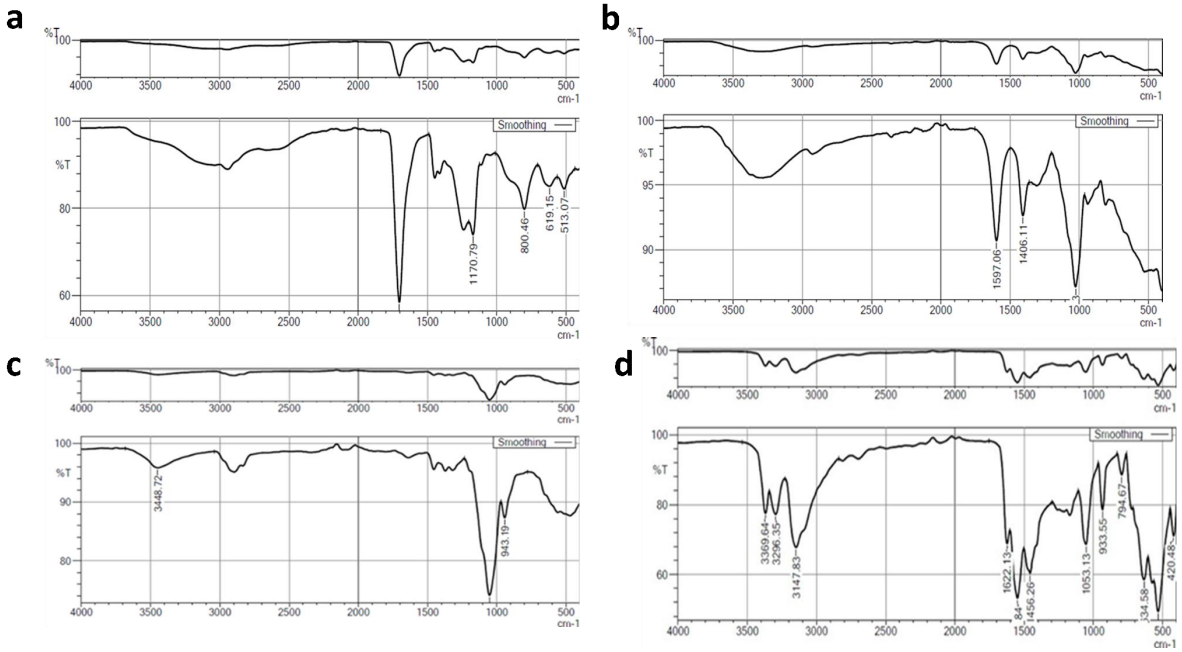

Figure 1: (a) IR spectral of Carbopol, (b) IR spectral of Sodium alginate, (c) IR spectral of HPMC K4M, (d) IR spectral of Metformin HCl.

The FT-IR analysis of Carbopol highlights distinct peaks corresponding to its functional groups: stretching vibrations of CH (2948.09 cm-1), C=O (1703.14 cm-1), and CH2 (1451.69 cm-1) indicate alkyl and carbonyl groups, while bending vibrations of C-H (1170.79 cm-1), O-H (800.46 cm-1), and N-H (619.15 cm-1) provide insights into its molecular configuration. In contrast, the FT-IR analysis of sodium alginate reveals stretching vibrations of O-H (3439.82 cm-1) and C-H (2926.43 cm-1), indicating hydroxyl and alkyl groups, along with carboxylate stretching (1597.06 cm-1 and 1406.11 cm-1) and C-O stretching (1026.13 cm-1) indicating carboxyl and pyranosyl ring presence. HPMC K4M displays notable peaks like O-H stretching (3448.72 cm-1) and CH2 stretching (2930.35 cm-1), C=C stretching (1647.24 cm-1), and Ar C-C stretching (1465.46 cm-1), along with C-O stretching (1320.91 cm-1) and bending vibrations (1053.13 cm-1 and 943.19 cm-1). Metformin HCl exhibits characteristic peaks such as N-H stretching (3369.64 cm-1), C-H stretching (2687.10 cm-1), C=O stretching (1622.13 cm-1), and C-N stretching (1548.84 cm-1), along with C-C stretching (1053.13 cm-1) and C-H bending (933.55 cm-1). These distinct peaks signify the unique molecular structures of each compound, facilitating their identification and characterization in pharmaceutical formulations and quality control analyses (Rojek & Wesolowski, 2019).

FTIR analysis of the mixture of Drug and Polymers

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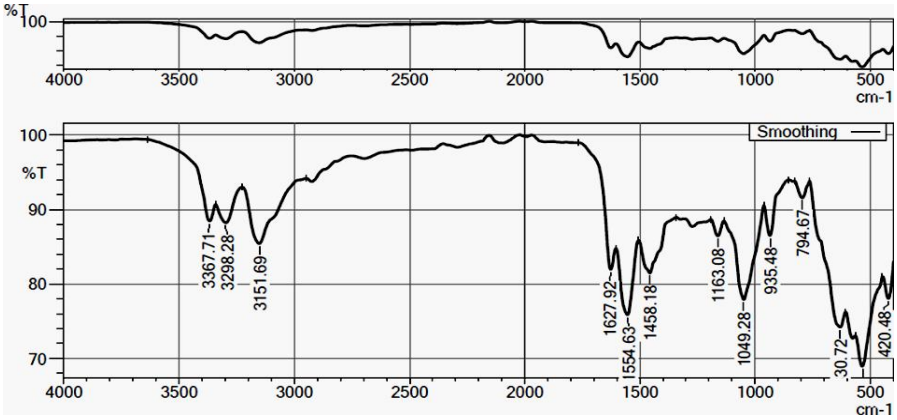

Figure 2: IR Spectra of Physical mixture of drug and Polymers

The FT-IR analysis of the physical mixture of drugs and polymers, as illustrated in Fig. 2, reveals crucial insights into component compatibility and molecular interactions. The presence of characteristic peaks corresponding to various functional groups in both drugs and polymers indicates their compatibility (Liu et al., 2004). Comparing the mixture's spectrum with individual spectra shows consistent intensities, positions, and base areas, with no emergence of new peaks. This absence of new peaks suggests a lack of significant chemical interactions or incompatibilities between the drugs and polymers. Consequently, this reinforces their suitability for pharmaceutical formulations. The comprehensive analysis aids in developing stable and effective formulations by deepening the understanding of molecular interactions and compatibility in drug-polymer systems.

Properties of the Floating Metformin HCl SR granules

Granule evaluation from batches M1 to M9 of Floating Metformin HCl SR before compression displayed favorable pre-compression parameters, as depicted in Table 2. All batches exhibited an angle of repose below 30 degrees, indicating good flow properties, while bulk densities ranged from 0.44 to 0.59 gm and tapped densities from 0.49 to 0.65 gm, suggesting adequate powder compaction. Carr's Index ranged from 8.06% to 14.28%, and Hausner's ratios from 1.09 to 1.16, both indicative of good flow properties (Saker et al., 2019). These findings collectively suggest excellent flow characteristics essential for downstream processing like tablet compression. Standard deviations (SD) reported ensure measurement consistency and reliability, with each parameter evaluated in triplicate (n=3).

Table 2: Properties of the Floating Metformin HCl SR Granules

Formulations Batch	Angle of repose±SD (°)	Bulk density±SD (gm)	Tapped density±SD (gm)	Carr's Index±SD	Hausner's ratio±SD
M1	26.52±0.2	0.44±0.03	0.49±0.02	10.20±0.41	1.11±0.3
M2	27.34±0.3	0.47±0.04	0.54±0.04	12.96±0.26	1.14±0.3
M3	29.23±0.4	0.51±0.02	0.59±0.03	13.56±0.32	1.15±0.6
M4	28.03±0.5	0.57±0.01	0.62±0.04	08.06±0.45	1.09±0.7
M4	29.01±0.2	0.59±0.05	0.65±0.05	09.23±0.76	1.10±0.1
M5	26.23±0.4	0.54±0.04	0.63±0.03	14.28±0.57	1.16±0.6
M6	28.52±0.3	0.49±0.02	0.54±0.02	09.26±0.25	1.10±0.2
M7	27.24±0.1	0.49±0.03	0.56±0.03	12.50±0.12	1.14±0.2
M8	29.13±0.2	0.49±0.02	0.54±0.02	09.26±0.25	1.10±0.4
M9	26.45±0.4	0.44±0.04	0.51±0.04	13.72±0.25	1.15±0.9

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Properties of the Floating Metformin HCl SR Tablets

The evaluation of Floating Metformin HCl SR tablets from batches M1 to M9, summarized in Table 3, indicates compliance with Pharmacopoeia standards, demonstrating stringent quality control measures during formulation. Tablet weights, ranging from 0.848g to 0.851g, show mass uniformity crucial for dosage accuracy, while hardness values (4 to 8.8 Kg/cm2) suggest adequate tablet strength. Friability percentages (0.20% to 0.42%) signify minimal tablet abrasion, preserving drug content, and drug content uniformity (98.56% to 99.82%) reflects precise drug distribution. Floating lag times (110 to 240 seconds) and total buoyancy over 10 hours ensure sustained drug release and therapeutic efficacy, highlighting the robustness and reliability of the formulations for optimal clinical performance and patient outcomes (Arora et al., 2005).

Table 3: Properties of the Floating Metformin HCl SR Tablets

Formulations	Tablet average weight ± SD (g)	Tablet Hardness ± SD (Kg/cm^2)	Friability± SD (%)	Content of Drug±SD (%)	Floating lag time (secs)	Total floating time (Hrs)*
M1	0.849±0.012	7.2±0.2	0.30±0.02	98.89±0.23	150±0.23	10
M2	0.851±0.021	7.4±0.3	0.25±0.04	99.52±0.31	220±0.23	10
M3	0.850±0.032	8.2±0.1	0.22±0.06	99.23±0.34	120±0.45	10
M4	0.848±0.022	8.4±0.2	0.20±0.01	98.56±0.25	125±0.35	10
M5	0.850±0.042	7.8±0.4	0.31±0.03	99.75±0.42	220±0.25	10
M6	0.849 ±0.011	6.8±0.3	0.42±0.02	99.30±0.62	110±0.32	10
M7	0.851±0.013	8.8±0.2	0.20±0.03	99.82±0.44	135±0.24	10
M8	0.849±0.014	7.0±0.5	0.39±0.05	98.89±0.54	205±0.06	10
M9	0.850±0.025	7.3±0.3	0.28±0.06	99.81±0.36	240±0.12	10

Swelling Index Analysis of Floating Metformin HCl Tablets

The swelling index analysis of Floating Metformin HCl SR formulations, as depicted in Figure 3, reveals a time-dependent increase in swelling propensity across all formulations, indicating their capacity for fluid absorption and sustained drug release through diffusion. Particularly, formulations containing higher viscosity polymers like M7 exhibit superior swelling indices of up to 112%, suggesting that polymers with elevated viscosity enhance swelling properties, potentially optimizing drug release kinetics, as supported by (Upadhyay et al., 2014) Furthermore, the in vitro release profile conducted with a USP dissolution apparatus (Basket type) supplements the swelling index data, offering a holistic understanding of the formulation's release behavior under simulated physiological conditions, collectively providing valuable insights into the performance and functionality of Floating Metformin HCl SR formulations.

Analysis of sustained release profile of Floating Metformin HCl SR tablets

The in vitro drug release profile of Floating Metformin HCl SR illustrated in Fig 4, offers valuable insights into the formulations' release kinetics over an 8-hour period. The cumulative drug release (CDR) percentages for formulations M1 to M9 ranged from 71.05% to 96.24%, indicating variations in drug release rates among different formulations. Notably, formulations M2, M5, M7, and M9 displayed CDR values exceeding 90%, suggesting their potential as sustained-release (SR) formulations with superior drug release characteristics suitable for floating bilayer tablets. The observed trends in drug release corresponded with the formulations' swelling indices, suggesting a correlation between swelling behavior and drug release kinetics. These findings underscore the importance of optimizing formulation

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parameters to achieve desired drug release profiles, ultimately enhancing the efficacy and therapeutic outcomes of Floating Metformin HCl SR formulations (Ahmed et al., 2016).

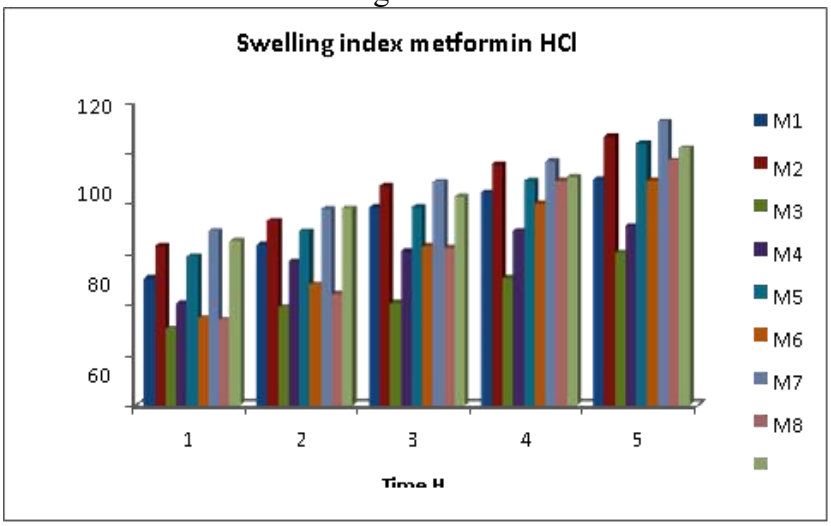

Figure 3: Swelling index profile for Floating Metformin HCl SR

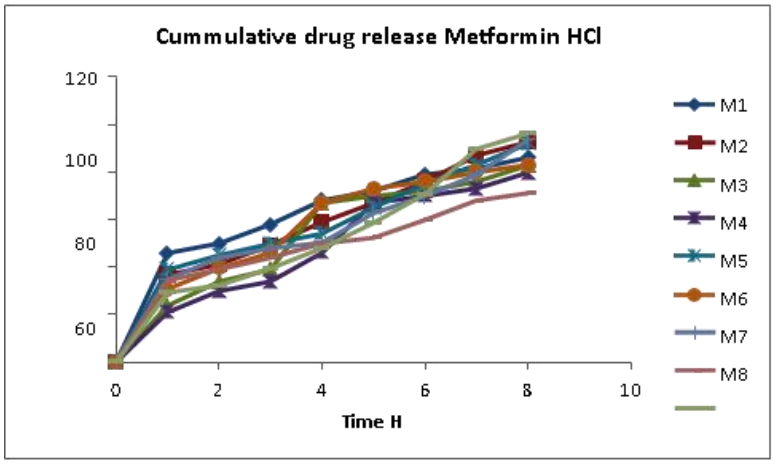

Figure 4: Invitro drug release profile of Floating Metformin HCl SR

CONCLUSION

The extensive examination of the interactions between Metformin HCl and various excipients has revealed their compatibility for tablet formulation. The favorable attributes observed in Floating Metformin HCl SR tablets, along with their compliance with Pharmacopoeia standards during physical assessment, signal a promising direction for tablet production. Additionally, the evaluation of swelling indices and drug release profiles underscores the potential of formulations incorporating both synthetic (HPMC) and natural (sodium alginate) polymers for floating bilayer tablets, offering prospects for enhanced therapeutic efficacy. This investigation provides valuable insights into the development of pharmaceutical formulations aimed at achieving superior clinical outcomes.

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