How to Cite:
Harika, S. K. M., Sudhakar, M., & Rao, V. V. B. (2022). Formulation and characterization of nimodipine in situ gels for oral delivery. *International Journal of Health Sciences*, *6*(S1), 5445–5463. https://doi.org/10.53730/ijhs.v6nS1.6102

Formulation and characterization of nimodipine *in situ* gels for oral delivery

S. K. Madhavi Harika
University college of Technology, Osmania University, Hyderabad, Telangana

M. Sudhakar
Malla Reddy College of Pharmacy, Hyderabad, Telangana

V. V. Basava Rao
University college of Technology, Osmania University, Hyderabad, Telangana

***Abstract*---**To formulate and evaluate Nimodipine floating *in situ* gels for oral delivery in order to enhance its residence time and to overcome the inherent drawbacks associated with conventional oral formulations like tablets and capsules. As Nimodipine is a BCS Class II drug, first Nimodipine solid dispersions were made to enhance its solubility. Solvent evaporation method was employed for this. Then in situ gel formulations were prepared using the optimized solid dispersion formulations. Sodium alginate and HPMC K100M were used as gelling agent and viscosifying agent respectively. In vitro characterization like gelling capacity, floating time, drug content, viscosity, % cumulative drug release studies were performed. In vivo pharmacokinetic parameters were studied. Infrared spectroscopy ruled out drug-excipient interactions. The release pattern showed a burst effect in the first 30 minutes followed by a moderate steady release for 12 hours. Stability testing indicated that the formulation remained stable with no significant changes in percent cumulative drug release and viscosity. *In vivo* pharmacokinetic study results were satisfactory. A promising, stable, sustained release, liquid oral floating *in-situ* gelling systems of Nimodipine were successfully developed and evaluated. Oral in situ gels could be good alternative for geriatric and pediatric population who have trouble swallowing solid medications.

***Keywords*---**Oral delivery, Floating *in-situ* gel, Nimodipine, *In vivo* Pharmacokinetic study, Sodium Alginate.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
***Corresponding author**: Harika, S.K.M.; Email: skmharika@gmail.com*
Manuscript submitted: 09 Feb 2022, Manuscript revised: 27 March 2022, Accepted for publication: 18 April 2022

Introduction

Tablets and capsules must be swallowed as whole and they cannot be cut in half for dosage adjustments because they are designed for sustained release. Bulky tablets and capsules are difficult for the elderly, pediatric and dysphagic people to swallow. So, oral in situ gels can be an alternative approach for this. High doses of medication can be added into liquid oral *in-situ* gelling formulations(Kanamala et al., 2016)(Pande et al., 2013).

The research on *in-situ* gel systems has got a lot of attention in recent years as they improve efficacy, patient compliance and convenience while reducing adverse effects, toxicity and frequency of dosage(Liu et al., 2006; Vipul and Basu, 2013; Xu et al., 2014). Gelling can occur in situ as a result of a single or a combination of stimuli such as pH changes, temperature modulation, or ionic exchange(Rao, 2012; Ravi Kumar, 2000; Uchida et al., 1992).

Before administration, the *in-situ* gel dosage form is a liquid, but once it gets in touch with gastric contents, it transforms into a gel that floats on top of it. Physiological stimuli (e.g., temperature and pH), physical changes in biomaterials (e.g., solvent diffusion and swelling) and chemical reactions (e.g., enzymatic, ionic and photo-initiated polymerization) are the factors that contribute to gel transformations(Javia et al., 2021; Suresh and Bhaskaran, 2005).

Nimodipine is a calcium channel blocker made from dihydropyridine that is used to treat hypertension, stroke, and cerebrovascular spasms. It is a BCS class II drug. The main issue with nimodipine is that it has low solubility and has a limited oral bioavailability (5–10%). It is mainly absorbed in the upper gastrointestinal tract. So, the development of floating in situ gel formulation will be beneficial(Pashikanti and Jyothsna, 2019).

In-situ gelling systems that undergo a phase change in the presence of various di and trivalent ions have been developed using a variety of natural and synthetic polymers, including polysaccharides like carrageenan, gellan gum, pectin, and sodium alginate(Qiu and Park, 2012; Qureshi et al., 2019). Sodium alginate is a hydrophilic natural polymer that can be utilized to entrap water-soluble pharmaceuticals(Mooranian et al., 2014; Prajapati et al., 2013; Rathod et al., 2014) and is commonly employed in pharmaceutical formulations(Artiga-Artigas et al., 2017; Kilicarslan et al., 2018). HPMC can be employed as a viscosity modifier.

The current study aims to design and evaluate oral, floating *in-situ* gel formulations of Nimodipine for sustained release. Sodium Alginate was used as gelling agent and HPMC K100M as viscosifying agent.

Material and Methods

Nimodipine was purchased from Gluchem Chemicals, Hyderabad; Telangana, Sodium Alginate was procured from Loba Chemicals Pvt. Limited; Mumbai, Calcium carbonate and sodium bicarbonate were purchased from SD Fine-Chem limited, Mumbai; HPMC K100M, PVP K30, Aerosil, Magnesium stearate, methanol

and Hydrochloric acid were purchased from Molychem; Mumbai, Sodium citrate was procured from Qualigens; Mumbai.

Methods

Preparation of Solid dispersions

Nine different solid dispersions were prepared by solvent evaporation method(Kubo et al., 2004). Solid dispersions of nimodipine with polymers PVP K30 and HPMC acetate succinate were prepared as shown in Table 1. The components were dissolved in methanol to get the solution. The solution was stirred using a magnetic stirrer until the solvent was evaporated and solid wet mass was dried in an oven at 45°C. After solidification, it was pulverized and sieved through sieve no. 40 and stored in a desiccator for further use(Jaipal et al., 2015).

Solubility Study of drug and solid dispersion

The solubility study of Nimodipine was carried out in various solvents. Accurately weighed 20 mg of drug was added to screw-capped vials containing 10 ml of solvent. The vials were kept in a water bath shaker at 37 ± 0.5 °C and shaken for 24 h. The mixtures were then filtered through a filter membrane of pore size 0.45 µm. The solubility studies of all the prepared solid dispersions were conducted in different media. Solubility of all Nimodipine solid dispersion formulations was determined in 0.1 N HCl and distilled water and assayed by double beam UV spectrophotometer (Lab India 3200) at λ_{max} 238 nm(Behera, A.L., Sahoo, S.K. and Patil, 2010).

Powder X-Ray Diffractometry [PXRD]

PXRD spectra of drug and solid dispersion systems were recorded using an X-ray diffractometer (Rigaku Analytical XRD, India). XRD studies were performed under the following conditions of CuK∞ line (λ = 0.154 nm), current 35 mA, voltage 40 Kv and 2θ degrees at room temperature(Srinivas and Singh, 2021).

Scanning Electron Microscopy (SEM)

The morphology studies of the solid dispersion formulations of Nimodipine was performed using Scanning Electron Microscope (JEOL, Tokyo, Japan). Dried samples of formulations were spread and adhered to a piece of aluminum and coated with a thin layer of platinum. The images were taken with SEM at 30 Kv (Mohammadi and Kumar, 2019).

Estimation of Drug Content

An amount equivalent to 50 mg of Nimodipine was carefully weighed and transferred to a 100 ml volumetric flask. The volume was then made up with 0.1 N HCl and shaken for 10 minutes to ensure complete drug solubility. The solution was then filtered. Then the absorbance was measured at 238 nm for Nimodipine in double beam UV-Visible spectrophotometer(Mohammadi and Kumar, 2019)(Behera, A.L., Sahoo, S.K. and Patil, 2010).

Preparation of Nimodipine in situ gel

Sodium alginate was taken to which trisodium citrate was added and stirred well. In another beaker, Calcium Carbonate and HPMC K100M is added and stirred well with required quantity of water. This solution was added to the above prepared solution to which the drug Nimodipine was added and made up with water(Patel and Patel, 2006). Nimodipine in situ formulations are shown in Table 2.

Physical Appearance and pH

All the in situ gel formulations were visually checked for their appearance. The pH of the *in situ* solution was measured using standardized digital pH meter (Lab India SAB 5000) at room temperature by taking adequate volume in a 50 ml beaker(Khan and Bajpai, 2010).

***In Vitro* Gelling Capacity**

The *in vitro* gelling capacity of the formulations was measured by placing 5 ml of the gelation solution (0.1N HCl, pH 1.2) in a 15 ml borosilicate glass test tube maintained at 37 ± 1°C temperature. The formulation (1 ml) was added slowly by placing the pipette at surface of fluid in the test tube. As the formulations come in contact with gelation solution, they are immediately converted into a stiff gel like structure. The gelling capacity of formulations was graded in three categories based on the stiffness of formed gel and time period for which the gel retained its rigidity(Nassour et al., 2014).
(+) Gels after five min, dispersed within 8 h
(++) Gels within 60 sec and retain gel structure for 12 h
(+++) Gels immediately and retains gel structure for more than 12 h

***In Vitro* Buoyancy test**

The *in vitro* buoyancy was characterized by floating lag time and total floating duration. This study was carried out using dissolution apparatus Type Ⅱ using 500 ml of 0.1N HCl (pH-1.2) as the medium. The test was carried out at 50 rpm at 37 ± 0.5 °C. The *in situ* gelling solution (10 ml) was transferred to a petri plate using a syringe. The plate was then placed on surface of the medium and plunged in to the medium with the moving paddle. The time required for the gelled mass to rise to the surface of the dissolution medium (floating lag time) and the duration of the time for which the gel constantly floated on the dissolution medium (floating duration) was noted for each formulation(Ahmed et al., 2017; Pandya et al., 2013; Swamy and Abbas, 2012).

Density

Density of the floating oral *in situ* gel was determined by using water displacement method(Rajinikanth et al., 2007). To 10 ml of *in situ* solution, 20 ml of 0.1N HCl was added to convert the solution into gel. Excess of HCl was drained and the gel so formed was weighed. The gel was then transferred to a 50 ml measuring cylinder and allowed to settle at the bottom. Distilled water was added up to 50 ml mark of the measuring cylinder. Volume of water was noted in the presence of gel. The

volume of gel was obtained from the difference in the volumes of water with and without gel i.e., amount of water displaced by gel was calculated by using the following formula,

$$d = m/v$$

Where, d = density, m = mass, v = volume

Viscosity

The viscosities of the solutions were determined by Brook field viscometer (RVDV-II+P). The samples (10 ml) were sheared at 100 rpm with S21 spindle at room temperature. Viscosity measurement for each sample was done in triplicate(Thomas, 2014).

Drug content

In situ solution (equivalent to 60 mg of Nimodipine) was taken in a volumetric flask. To this 50 ml of 0.1 N HCl was added and shaken on mechanical shaker for 30 min. This was followed by sonication for 15 min for complete dispersion of contents and filtration using 0.45 µm membrane filters. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1 N HCl. Content of Nimodipine was determined spectrophotometrically at 238 nm using double beam UV-visible spectrophotometer (Lab India 3200)(Miyazaki et al., 2001).

***In Vitro* Drug release studies**

The drug release study was carried out using USP Type Ⅱ apparatus at 37 ± 0.5°C and at 50 rpm using 900 ml of a dissolution medium having 0.1N HCl. *In situ* gel equivalent to 60 mg of Nimodipine (5 ml) was poured into the dissolution bowl after attaining 37±0.5°C. 5 ml of sample solutions were withdrawn at 30 min, 1 h, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h and replaced with fresh medium. Withdrawn samples were filtered through 0.45 µm membrane filter and diluted suitably with 0.1N HCl (pH 1.2). Filtered samples were analyzed by UV-VIS spectrophotometer at 238 nm. The dissolution studies were carried out for a period of 12 h(Geethalakshmi et al., 2013; Patel et al., 2011).

FTIR

In FTIR studies, infrared spectra were obtained using FTIR spectrophotometer (Bruker). The previously grounded samples (Nimodipine, HPMC K100M, Sodium Alginate, *In situ* gel physical mixture) were mixed separately with KBr powder and were compressed into discs. The range of scanning was kept at 4000-500 cm^{-1}(Behera, A.L., Sahoo, S.K. and Patil, 2010).

***In vivo* Pharmacokinetic Study**

Eighteen male albino rabbits of body weight 1.5 kg were selected from the animal house. The animals, housed in standard cages in a light-controlled room at 19±1

^{0}C and 50±5% R.H., were fed with standard pellet diet and water ad libitum. All the studies were conducted in accordance with the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The procedures involving animals were reviewed and approved by the Animal Ethical Committee at Jeeva Life Sciences Hyderabad, India. (CPCSEA/IAEC/JLS/16/07/21/46).

The animals were divided into 3 groups having 6 animals in each group for the test optimized in situ gel formulation, aqueous suspension of Nimodipine and optimized solid dispersion formulation. All animals were maintained for a wash-out period of 15 days before the study. Nimodipine dose was calculated as 4.62 mg for each rabbit of weight approx. 1.5 Kg. The dose for rabbit was calculated as follows:

Average animal dose (mg)=AED *weight of the animal/1000

Where, AED=Animal equivalent dose (mg/kg)

The in situ gel formulation, solid dispersion formulation and aqueous suspension of Nimodipine were administered in the form of dispersion to six male rabbits each in three groups using oral feeding tube. At different time points (0.5, 2, 4, 8, 12, and 24 h), a blood sample of 0.5 ml was withdrawn from the marginal ear vein of the rabbit. Plasma was separated by centrifugation process at 5000 rpm for 5min and stored under frozen condition until the analysis performed. Samples were analyzed by HPLC. From the obtained peak area values, plasma concentrations were determined and graph was plotted by taking plasma concentration on Y-Axis and time on X-Axis. Various pharmacokinetic parameters like elimination rate constant (K), peak plasma concentration (C_{max}), time to attain the peak plasma concentration (T_{max}), area under the curve (AUC), and area under the first moment curve (AUMC) were calculated(Shoaeba et al., 2021).

Stability studies

Stability studies of the optimized Nimodipine in situ gel formulation were conducted for 6 months according to ICH guidelines. The formulations were stored at 40 ℃ ±2 ℃/75%±5% RH in a stability chamber (SC-10 PLUS, REMI Elektrotechnic, Mumbai, India) for 6 months. The *in-situ* gel was analysed for change in physical appearance, drug content, floating time and % cumulative drug release after a period of 0, 30, 90, and 180 days(Maheswaran et al., 2017; Mathews et al., 2019).

Results and Discussion

Saturation Solubility Studies

The saturation solubility of drugs and Solid dispersions in different media is presented in Fig. 1&2. SDN1-SDN9 showed increased solubility compared to pure Nimodipine. Another observation revealed that Solid dispersions in 0.1N HCl showed high solubility than in distilled water. On contact with dissolution medium, the hydrophilic polymer dissolves and the drug is converted into fine colloidal particles. This state causes enhanced dissolution due to the higher surface area of the colloidal particles(Maheswaran et al., 2017).

Compatibility studies

Compatibility studies were done using FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and different polymers were studied. FTIR technique has been used to study the physical and chemical interaction between drug and excipients used. It has been observed that there is no chemical interaction between drug and the polymers used in the stud. The pure drug Nimodipine contains a pyridine N-H group shows an absorption peak at 3313 cm^{-1}. The C-H peaks were seen at 3081 cm^{-1} due to the presence of aromatic ring system. The aliphatic absorption peak of C-H were seen at 2973 cm^{-1} the carboxylate absorption of C = O gives a distinct peak at 1695 cm^{-1} this data is in full agreement with the structure of the drug used which is nimodipine during the present research work. All the functional group absorbance bands of Nimodipine can be satisfactorily found in the range for Optimized formulation mixture(Hou et al., 2013). FTIR results are shown in Fig. 3 and Table 3.

Estimation of Drug Content

The % drug content was found for all solid dispersion formulations and are shown in Table 4. Among all solid dispersion formulations drug content was found to be more in SDN 1.

Scanning Electron Microscopy (SEM)

The morphology of SDN 1, 3, 7, and 9 solid dispersions was seen using SEM examination. The SDN1 samples had crystal like structures, but the remaining solid dispersion formulations had showed irregular bulk form. (Patel et al., 2011; Shoaeba et al., 2021). SEM images were depicted in Fig.4.

Powder X-Ray Diffractometry [PXRD]

XRD of Nimodipine showed characteristic peaks at various diffraction angles (2θ) at 13.1°, 25.5°, 19°, 9.2°, which confirmed its crystalline nature and is shown in Fig.5. The XRD pattern of the SDN1 showed characteristic diffraction peaks at 13.1°, 25.5°, 19°, 9.2°, but with lesser intensity. However, the absence of sharp diffraction peaks was observed in all SDs which indicate the formation of solid dispersion(Hou et al., 2013).

Physical appearance, pH and drug content of in situ gels

The Physical appearance, pH and drug content of in situ gels were shown in table 5. All the formulations were found to be clear, white colored solutions. The pH level was within safe limits (6.0 to 6.9). The drug content of the *in-situ* gels was in the range of 98-99 % w/w, ruling out any chance of drug or additive segregation during formulation.

***In vitro* gelling capacity**

In vitro gelling capacity of various formulations of ion sensitive floating oral *in situ* gels was reported in Table 5. The *in situ* gel should maintain its integrity without dissolving or eroding for an extended time. After ingestion, the liquid polymeric solution of sodium alginate undergoes a rapid sol-to-gel transition by means of ionic gelation. The gelation involves formation of double helical junction zone followed by aggregation of the double helical segments to form a three dimensional network by complexation with Ca^{+2} ions and hydrogen bonding with water. It was observed that formulations F5–F15 showed immediate gelation on contact with acidic environment and retained gel structure for more than 12 h.

Buoyancy test

The buoyancy ability of the formulations was evaluated in 0.1 N HCl (pH 1.2). The time for the formulation to emerge on the surface of the medium is floating lag time and the time for which the formulation constantly floated on the dissolution medium surface is duration of floating. On contact with acidic medium, the calcium ions react with sodium alginate and produce a crosslinked three-dimensional gel network. Further carbon dioxide is released and is entrapped in gel network imparting buoyancy to the formulations(Patel et al., 2011)· All the formulations showed a reduction in floating lag time with increase in polymer concentration. The formulations containing high concentration of HPMC K100M exhibited lower floating lag time in the range of 82-145s. The formulations containing low concentration of the polymer displayed higher floating lag time. The values are depicted in Table 5.

Density

The main requirement of any floating system is that it must have density lesser than gastric contents (~1.004 gm/cm^3). The density of all floating *in situ* gel formulations were found to be less than that of gastric contents. This can clearly be a pointer to the floatability of the formulations. The average densities of all the formulations were found to be 0.694 to 0.869 gm/cm^3.

Viscosity

The rheological properties of the solutions are of importance in view of their proposed oral administration. The solutions showed a marked increase in viscosity with increasing concentration of Sodium alginate. Increase in the sodium alginate and HPMC K100M concentration in the formulation simultaneously increased the viscosity at all polymer concentration studied. The average viscosities of all formulations were found to be in the range of 74 to 236 cps. The values are given in Table 5.

***In vitro* drug release**

The impact of polymer concentration on *in vitro* drug release from *in situ* gels is depicted. A significant decrease in rate and extent of drug release was observed with the increase in polymer concentration and is attributed to increase in the polymer matrix density and also increase in the diffusional path length which the drug molecules have to traverse. The release of the drug from these gels is characterized by initial phase of high release (burst effect) followed by a slower release as the gelation proceeds. This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics. A similar release profile was evident with all the formulations releasing 20 - 35% drug in the first 30 min followed by a more gradual release. It was observed that formulation F12 with concentration of sodium alginate i.e. [280 mg] and HPMC K 100M [200 mg] show sustained release of upto 99.7 % in 12 h. It was observed that as the polymer concentration increased, the retarding effect on the release of the formulation got stronger. The formulations containing higher concentration of sodium alginate and HPMC K100M released their contents for longer period of times at slower rates hence showing sustained release effect. Results are shown in Fig. 6.

***In vivo* studies**

To determine the plasma levels of Nimodipine after oral administration, in vivo pharmacokinetic investigations were performed with Nimodipine pure drug suspension, optimized solid dispersion and optimized in situ gel formulation. Table 6 displays each pharmacokinetic parameters individually. Figure 7 displays the concentration in plasma versus time graph of in situ gel, solid dispersion and pure drug suspension. The increase of Tmax value for in Situ gel formulation (7 ± 0.002 h) compared to that of pure drug suspension (4 ± 0.01 h) and solid dispersion (4 ± 0.01 h) indicates delayed absorption and slow release of drug from in situ gels. Increased AUC of in situ gels (31647 ± 15.02 ng h/ml) compared to that of pure drug suspension (13224 ± 25.11 ng h/ml) suggests increased exposure to the drug. The AUC of solid dispersion (15678 ± 12.14) was also increased in comparision to pure drug but not as that of in situ gel. The small AUC obtained for pure suspension and solid dispersion indicates the rapid clearance of the drug from the plasma. Moreover, the Cmax of nimodipine in situ gel was higher when compared to pure suspension. (4213 ± 0.011 ng/ml and 2901 ± 0.021 ng/ml respectively). This suggests higher absorption. Cmax of solid dispersion (3192 ± 0.312) was more than pure drug but less than in situ gel. The in situ gel's plasma profile showed a continuous rise in drug concentration that peaked at 7 hours, then another gradual drop in plasma concentration.

Stability studies

Stability studies were carried out for the optimized formulation as per ICH guidelines (Q1C) revealed no significant changes in the physicochemical properties, gelling capacity, or drug release of the formulation even on the aging of the *in-situ* gel. Values are shown in Table 7.

Table 1: Formulation chart of Nimodipine solid dispersions

Ingredient	SDN 1	SDN 2	SDN 3	SDN 4	SDN 5	SDN 6	SDN 7	SDN 8	SDN 9
Nimodipine (mg)	60	60	60	60	60	60	60	60	60
PVP K 30 (mg)	240	220	200	180	160	140	120	100	80
HPMC acetate succinate (mg)	30	30	30	30	30	30	30	30	30
Aerosil (mg)	3	3	3	3	3	3	3	3	3
Methanol (ml)	30	30	30	30	30	30	30	30	30

Table 2: Formulation chart of floating *in-situ* gels of Nimodipine

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
SDN1(g)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Sodium Alginate (mg)	60	80	100	120	140	160	180	200	220	240	260	280	300	320	340
HPMC K100 (mg)	100	150	200	100	150	200	100	150	200	100	150	200	100	150	200
Calcium Carbonate (mg)	350	350	350	350	350	350	350	350	350	350	350	350	350	350	350
Trisodium Citrate (mg)	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Deionized water (ml)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Table 3: FTIR studies of Nimodipine in situ gels

Functional group	Bond nature	Characteristic wave number range	Wave numbers of pure drug	Wave numbers of optimized formulation
N – H	Stretching	3300 - 3500	3313 cm^{-1}	3266 cm^{-1}
C - H (aromatic)	Stretching	3010 - 3100	3081 cm^{-1}	3081 cm^{-1}
C = O	Stretching	1670 - 1820	1695 cm^{-1}	1724 cm^{-1}
NO_2	Stretching	1515 - 1560	1523 cm^{-1}	1519 cm^{-1}
C = C	Stretching	1620 - 1680	1648 cm^{-1}	1620 cm^{-1}
C – N	Stretching	1080 - 1360	1205 cm^{-1}	1196 cm^{-1}
C - H (aliphatic)	Stretching	2850 - 3000	2973 cm^{-1}	2973 cm^{-1}

Table 4: Drug Content in Nimodipine Solid dispersions

Formulation	% Drug Content
SDN1	99.11±0.11
SDN2	97.11±0.15
SDN3	98.14±0.11
SDN4	95.01±0.14
SDN5	96.45±0.11
SDN6	93.34±0.17
SDN7	92.24±0.13
SDN8	95.02±0.16
SDN9	93.47±0.11

Table 5: *In vitro* characterization of Nimodipine in situ gel formulations

Formula -tion	Clarity	pH	Gelling Capacity	Floating lag time (sec)	Total floating duration (h)	Drug Content (%)	Viscosity (cps)
F1	Clear	6.8±.02	++	171.01	>12	98.13±8.02	74±9.12
F2	Clear	6.2±.01	++	159.01	>12	99.25±1.02	80±6.02
F3	Clear	6.4±.01	++	141.47	>12	99.01±6.11	91±8.02
F4	Clear	6.2±.03	++	164.11	>12	99.42±5.12	100±8.12
F5	Clear	6.9±.02	+++	145.47	>12	99.65±4.11	108±9.13
F6	Clear	6.1±.04	+++	121.45	>12	99.21±8.01	111±8.32
F7	Clear	6.4±.06	+++	126.04	>12	99.44±6.14	126±8.02
F8	Clear	6.4±.02	+++	114.14	>12	99.62±5.02	138±6.02
F9	Clear	6.5±.01	+++	107.14	>12	99.47±8.32	142±8.37
F10	Clear	6.7±.04	+++	99.54	>12	99.88±6.02	165±8.14
F11	Clear	6.3±.01	+++	87.01	>12	99.56±4.03	175±6.02
F12	**Clear**	**6.4±.04**	**+++**	**84.47**	>12	**99.91±7.02**	**180±7.02**
F13	Clear	6.0±.01	+++	90.47	>12	99.88±4.02	198±5.02
F14	Clear	6.6±.02	+++	83.37	>12	98.68±7.12	215±8.11

F15	Clear	6.8±.03	+++	82.45	>12	99.89±6.02	236±6.02

Where, (+) Gels after five min, dispersed within 8h; (++) Gels within 60 sec and retain gel structure for 12 h; (+++) Gels immediately and retains gel structure for more than 12 h.

Table 6: Pharmacokinetic Parameters

Parameter	**Nimodipine Pure drug Suspension**	**Nimodipine in situ gel**	**Nimodipine solid dispersion**
C_{max} (ng/ml)	2901±0.021	4213±0.011	3192±0.312
T_{max} (h)	4±0.001	7±0.002	4±0.001
K (h)	0.309±0.013	0.11±0.011	0.3±0.012
AUC (ng-hr/ml)	13224±25.11	31647±15.02	15678±12.14
AUMC (ng-hr/ml)	64453±56.02	195382±41.04	78365±39.09
MRT	4.83±0.14	6.17±0.11	5.01±0.12

Table 7: Stability Study Data

Formulation	Parameter	Days			
		0	30	90	180
Optimized in situ gel formulation (F12)	Physical Appearance	Clear	Clear	Clear	clear
	Drug content (%)	99.91±7.02	99.67±1.11	99.58±1.24	98.09±1.68
	Floating Lag time (sec)	174.47±1.25	189.01±1.04	190.12±1.64	190.24±1.03
	% CDR	99.7±1.18	98.31±1.04	98.26±1.65	98.17±1.84

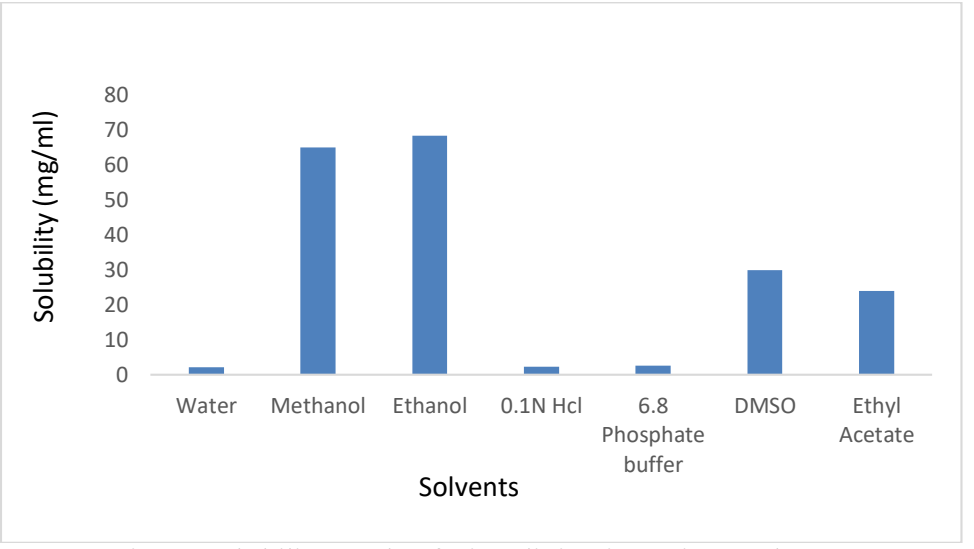

Fig. 1: Solubility study of Nimodipine in various solvents

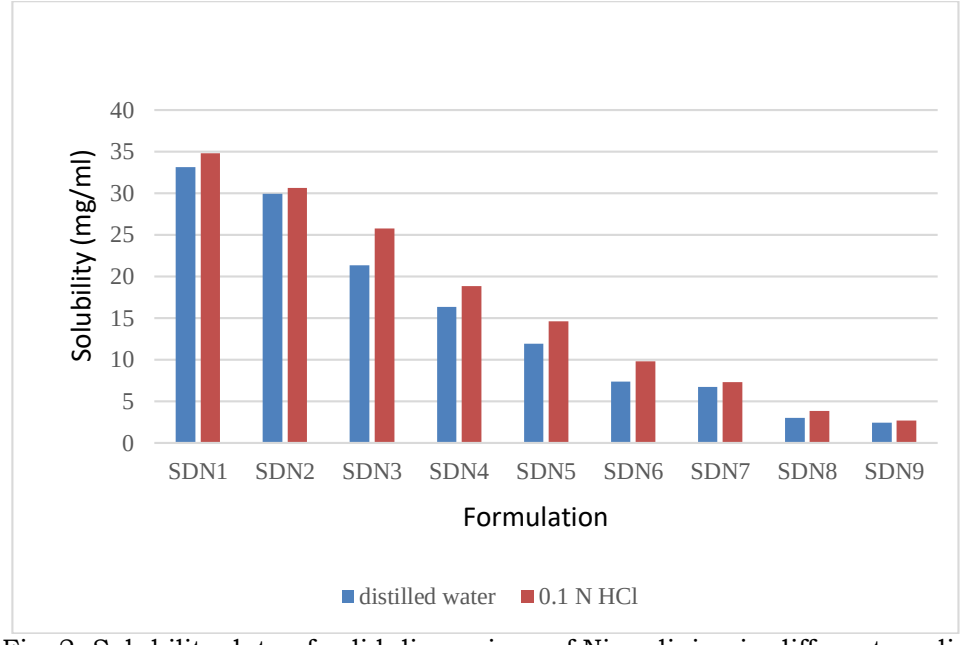

Fig. 2: Solubility data of solid dispersions of Nimodipine in different media

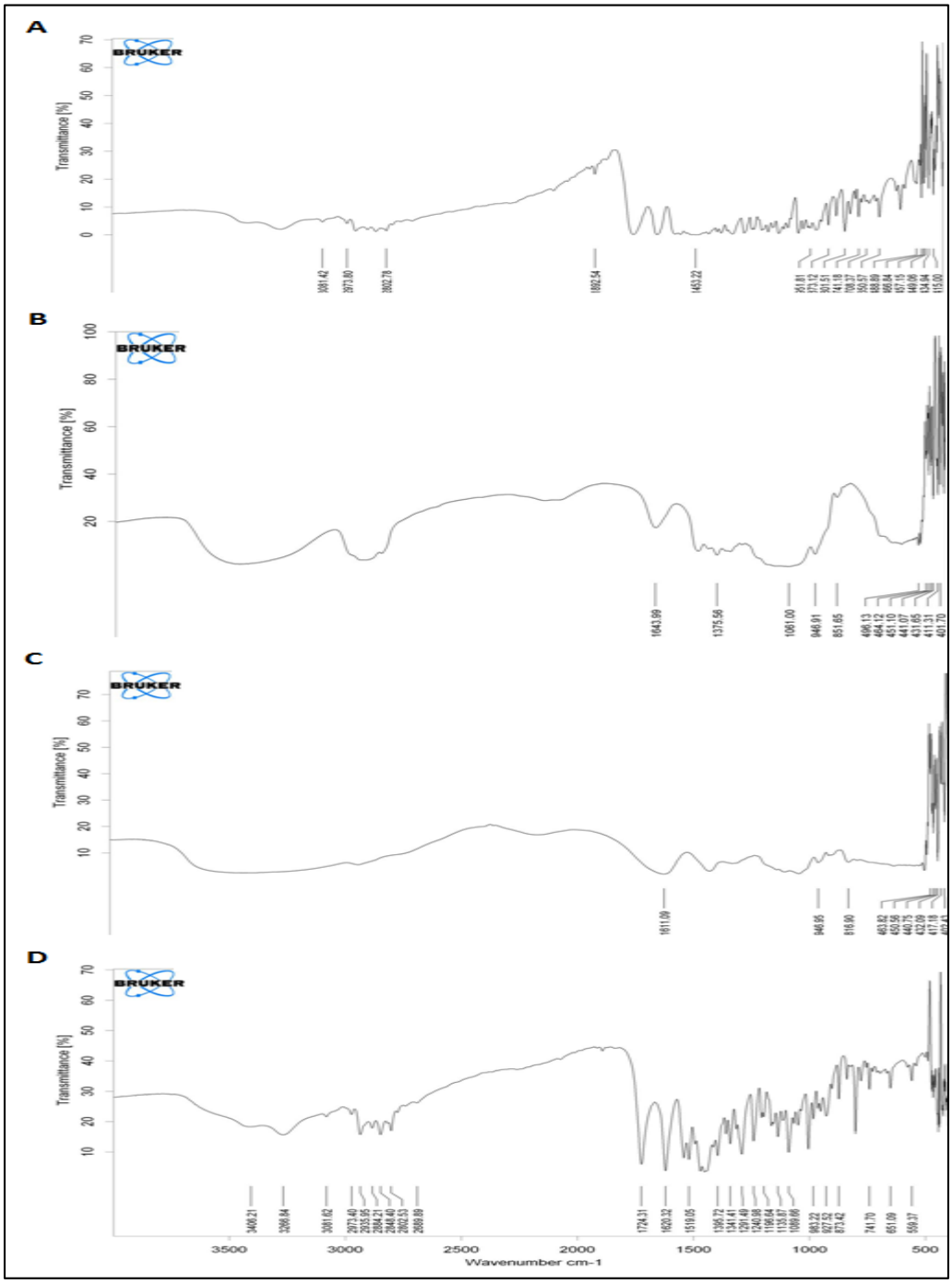

Figure 3: FTIR Spectra of (A) Nimodipine (B) HPMC K100M (C) Sodium Alginate (D) Optimized formulation

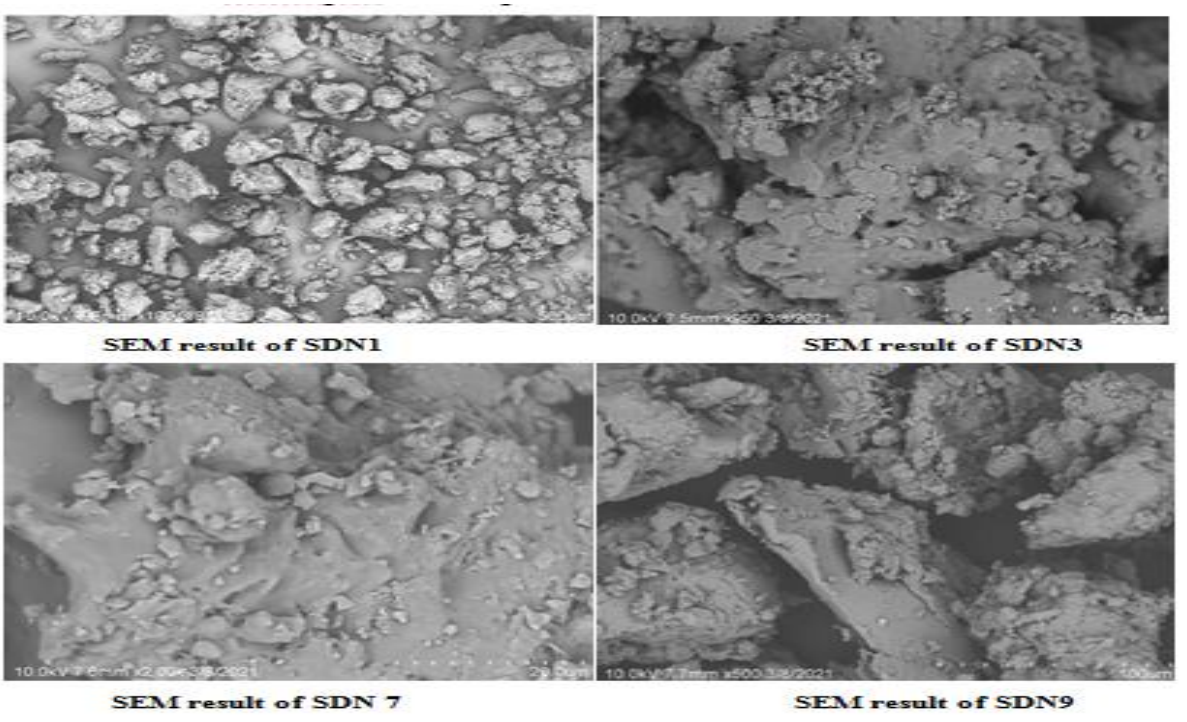

Fig 4: SEM images of Solid dispersions (SDN 1, 3, 7 & 9)

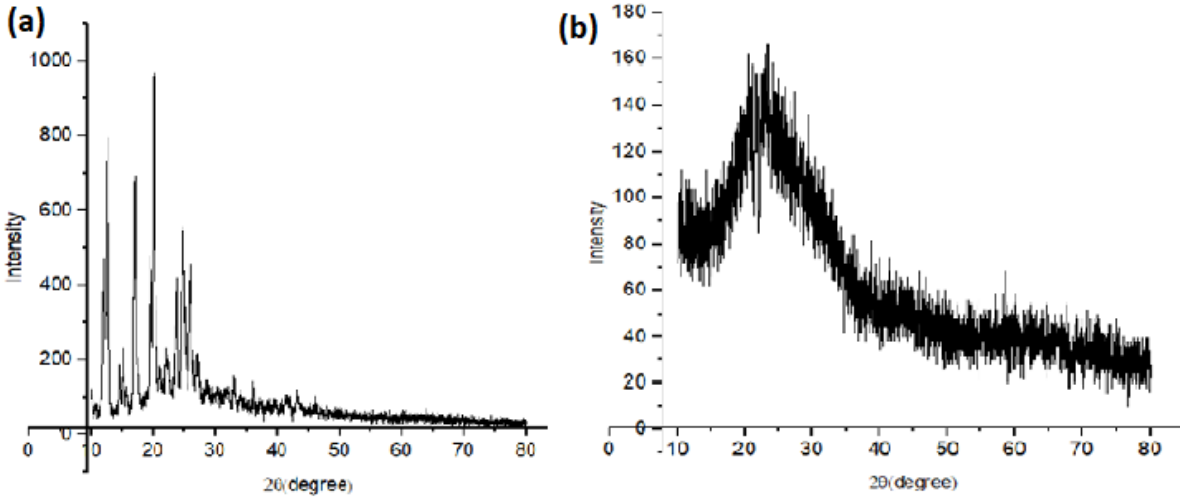

Fig 5: XRD spectra of (a) Nimodipine (b) Nimodipine Solid dispersion (SDN1)

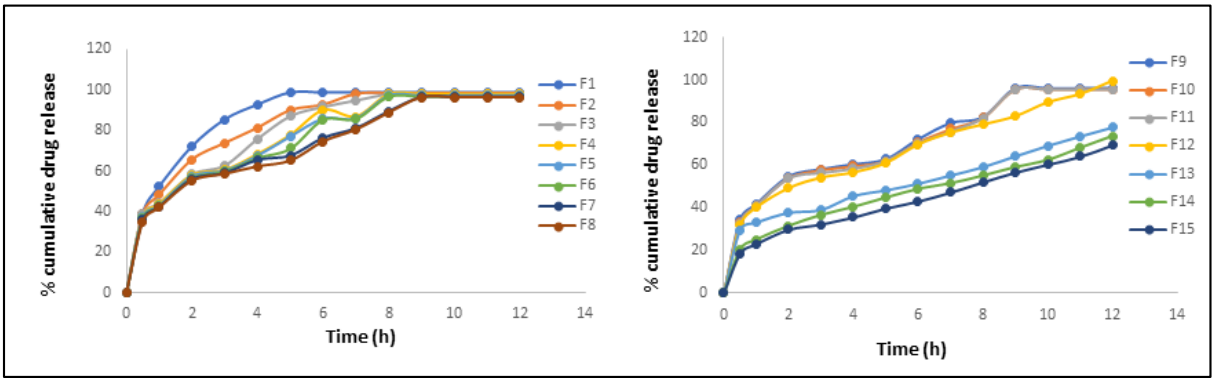

Fig. 6: % CDR of *in-situ* formulations of nimodipine

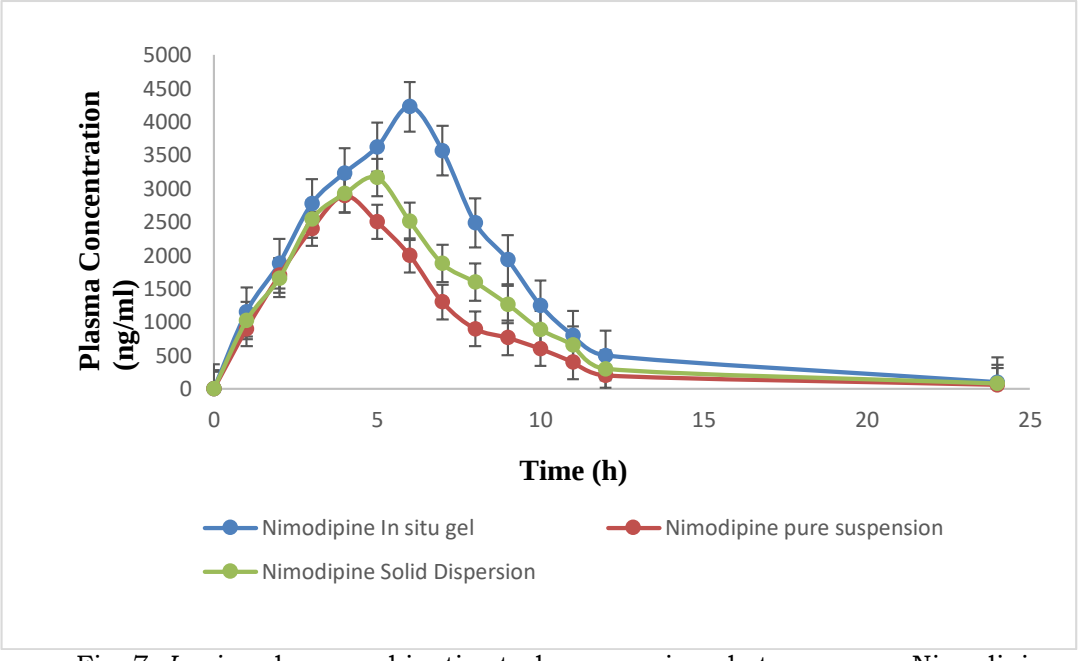

Fig. 7. *In vivo* pharmacokinetic study comparison between pure Nimodipine suspension, optimized in situ gel and optimized solid dispersion

Conclusion

Nimodipine oral in situ gels were formulated successfully in the study using sodium alginate and HPMC K100M as gelling agent and viscosifying agent respectively. The developed gels showed satisfactory gelling properties, pH, clarity, viscosity, release profile and in vivo pharmacokinetic parameters. Therapeutic concentrations of the drug could be achieved in plasma in a sustained manner and the drug release was for 12 h.

Acknowledgement

Authors are thankful to Malla Reddy College of pharmacy and Osmania University, Hyderabad, India for providing facilities to carry out this research work.

References

Ahmed, M.G., Kapoor, C., Adinarayana, S., 2017. Formulation and evaluation of oral sustained in situ gelling system of roxatidine. Indones. J. Pharm. 28, 179–184. https://doi.org/10.14499/indonesianjpharm28iss3pp179

Artiga-Artigas, M., Acevedo-Fani, A., Martín-Belloso, O., 2017. Effect of sodium alginate incorporation procedure on the physicochemical properties of nanoemulsions. Food Hydrocoll. 70, 191–200. https://doi.org/10.1016/j.foodhyd.2017.04.006

Behera, A.L., Sahoo, S.K. and Patil, S.V., 2010. Enhancement of solubility: A pharmaceutical overview. Der Pharm. Lett. 2, 310–318.

Geethalakshmi, A., Karki, R., Sagi, P., Jha, S.K., Venkatesh, D.P., 2013. Temperature triggered in situ gelling system for betaxolol in glaucoma. J. Appl. Pharm. Sci. 3, 153–159. https://doi.org/10.7324/JAPS.2013.30227

Hou, P., Ni, J., Cao, S., Lei, H., Cai, Z., Zhang, T., Yu, F., Tan, Q., 2013. Preparation and evaluation of solid dispersions of a new antitumor compound based on early-stage preparation discovery concept. AAPS PharmSciTech 14, 629–638. https://doi.org/10.1208/s12249-013-9948-y

Jaipal, A., Pandey, M.M., Charde, S.Y., Raut, P.P., Prasanth, K. V., Prasad, R.G., 2015. Effect of HPMC and mannitol on drug release and bioadhesion behavior of buccal discs of buspirone hydrochloride: In-vitro and in-vivo pharmacokinetic studies. Saudi Pharm. J. 23, 315–326. https://doi.org/10.1016/j.jsps.2014.11.012

Javia, A., Kore, G., Misra, A., 2021. Polymers in Nasal Drug Delivery: An Overview, in: Applications of Polymers in Drug Delivery. pp. 305–332. https://doi.org/10.1016/b978-0-12-819659-5.00011-2

Kanamala, M., Wilson, W.R., Yang, M., Palmer, B.D., Wu, Z., 2016. Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery: A review. Biomaterials 85, 152–167. https://doi.org/10.1016/j.biomaterials.2016.01.061

Khan, A.D., Bajpai, M., 2010. Floating drug delivery system: An overview. Int. J. PharmTech Res. 2, 2497–2505. https://doi.org/10.52711/2231-5659.2021.00046

Kilicarslan, M., Ilhan, M., Inal, O., Orhan, K., 2018. Preparation and evaluation of clindamycin phosphate loaded chitosan/alginate polyelectrolyte complex film as mucoadhesive drug delivery system for periodontal therapy. Eur. J. Pharm. Sci. 123, 441–451. https://doi.org/10.1016/j.ejps.2018.08.007

Kubo, W., Konno, Y., Miyazaki, S., Attwood, D., 2004. In situ gelling pectin formulations for oral sustained delivery of paracetamol. Drug Dev. Ind. Pharm. 30, 593–599. https://doi.org/10.1081/DDC-120037490

Liu, Z., Li, J., Nie, S., Liu, H., Ding, P., Pan, W., 2006. Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin. Int. J. Pharm. 315, 12–17. https://doi.org/10.1016/j.ijpharm.2006.01.029

Maheswaran, A., Padmavathy, J., Nandhini, V., Saravanan, D., Angel, P., 2017. Formulation and evaluation of floating oral in situ gel of diltiazem hydrochloride. Int. J. Appl. Pharm. 9, 50–53. https://doi.org/10.22159/ijap.2017v9i1.15914

Mathews, R., Prakash Rao, B., Konde, A., Sudarshan, S., Taha, N.A., Suresh, C., 2019. Statistical design and development of a liquid oral floating in situ gel of metformin hydrochloride for sustained release: Pharmacodynamic and toxicity (histopathology) studies. Int. J. Appl. Pharm. 11, 96–104. https://doi.org/10.22159/ijap.2019v11i5.30793

Miyazaki, S., Suzuki, S., Kawasaki, N., Endo, K., Takahashi, A., Attwood, D., 2001. In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. Int. J. Pharm. 229, 29–36. https://doi.org/10.1016/S0378-5173(01)00825-0

Mohammadi, H., Kumar, V.H., 2019. Formulation and Evaluation of Solid Dispersion Incorporated Fast Disintegrating Tablets of Tenoxicam Using Design of Experiment. Int. J. Pharm. Sci. Drug Res. 11. https://doi.org/10.25004/ijpsdr.2019.110106

Mooranian, A., Negrulj, R., Mathavan, S., Martinez, J., Sciarretta, J., Chen-Tan, N., Mukkur, T.K., Mikov, M., Lalic-Popovic, M., Stojancĕvić, M., Golocorbin-Kon, S., Al-Salami, H., 2014. Stability and release kinetics of an advanced gliclazide-cholic acid formulation: The Use of artificial-cell microencapsulation in slow release targeted oral delivery of antidiabetics. J. Pharm. Innov. 9, 150–157. https://doi.org/10.1007/s12247-014-9182-5

Nassour, L., Hasan, I., El-Hammadi, M., Abboud, H., 2014. Floating in-situ-gelling gellan formulations of metformin hydrochloride. J. Chem. Pharm. Res. 6, 1509–1517.

Pande, S.D., Vaidya, K.P. V., Gulhane, K.P.N., 2013. Floating Drug Delivery System (FDDS): A New Way for Oral drug delivery system. Int. J. Pharm. Clin. Sci. 3, 1–13.

Pandya, K., Aggarwal, P., Dashora, A., Sahu, D., Garg, R., Pareta, L.K., Menaria, M., Joshi, B., 2013. Formulation and Evaluation of Oral Floatable in-Situ Gel of Ranitedine Hydrochloride. J. Drug Deliv. Ther. 3. https://doi.org/10.22270/jddt.v3i3.516

Pashikanti, S., Jyothsna, B., 2019. Formulation and evaluation of floating in situ gel of ciprofloxacin. Int. J. Appl. Pharm. 11, 198–204. https://doi.org/10.22159/ijap.2019v11i1.28603

Patel, D.M., Patel, D.K., Patel, C.N., 2011. Formulation and Evaluation of Floating Oral In Situ Gelling System of Amoxicillin . ISRN Pharm. 2011, 1–8. https://doi.org/10.5402/2011/276250

Patel, M., Patel, D., 2006. Fast dissolving valdecoxib tablets containing solid dispersion of valdecoxib. Indian J. Pharm. Sci. 68, 222–226. https://doi.org/10.4103/0250-474X.25719

Prajapati, V.D., Jani, G.K., Zala, B.S., Khutliwala, T.A., 2013. An insight into the emerging exopolysaccharide gellan gum as a novel polymer. Carbohydr. Polym. 93, 670–678. https://doi.org/10.1016/j.carbpol.2013.01.030

Qiu, Y., Park, K., 2012. Environment-sensitive hydrogels for drug delivery. Adv. Drug Deliv. Rev. 64, 49–60. https://doi.org/10.1016/j.addr.2012.09.024

Qureshi, D., Nayak, S.K., Maji, S., Anis, A., Kim, D., Pal, K., 2019. Environment sensitive hydrogels for drug delivery applications. Eur. Polym. J. 120. https://doi.org/10.1016/j.eurpolymj.2019.109220

Rajinikanth, P.S., Balasubramaniam, J., Mishra, B., 2007. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. Int. J. Pharm. 335, 114–122. https://doi.org/10.1016/j.ijpharm.2006.11.008

Rao, G.U., 2012. International Journal of Comprehensive Pharmacy Buoyant Sustained Release Drug Delivery Systems Current Potentials Advancements and Role of Polymers : a Review. Pharm. Glob. 03, 1–5.

Rathod, H.J., Mehta, D.P., Yadav, J.S., 2014. A review on stomach specific floating in-situ gel. Int. J. Pharm. Res. 6, 19–30.

Ravi Kumar, M.N., 2000. Nano and microparticles as controlled drug delivery devices. J. Pharm. Pharm. Sci. 3, 234–258.

Shoaeba, S., Sharav, D., Hitesh, J., Asit, S., Meshram, D.B., 2021. Formulation and Evaluation of in Situ Ophthalmic Gel. J. Chem. Pharm. Res. 9, 25–29.

Srinivas, M., Singh, A., 2021. Enhancement of Solubility and Dissolution Rate of BCS Class-II Fluvoxamine Tablets using Solvent Evaporation Solid Dispersion Technique. J. Pharm. Res. Int. 44–53. https://doi.org/10.9734/jpri/2021/v33i31b31689

Suresh, S., Bhaskaran, S., 2005. Nasal drug delivery: An overview. Indian J. Pharm. Sci. 67, 19–25.

Swamy, N.G.N., Abbas, Z., 2012. Mucoadhesive in situ gels as nasal drug delivery systems: An overview. Asian J. Pharm. Sci. 7, 168–180.

Thomas, L.M., 2014. Formulation and evaluation of floating oral in-situ gel of metronidazole. Int. J. Pharm. Pharm. Sci. 6, 265–269.

Uchida, T., Yasutake, T., Goto, S., 1992. Utility of Mixture of Commercially Available Polymers as Constituents of Sustained-Release Microcapsules Containing Cefadroxil or Theophylline1e. Chem. Pharm. Bull. 40, 463–466. https://doi.org/10.1248/cpb.40.463

Vipul, V., Basu, B., 2013. Formulation and characterization of novel floating in-situ gelling system for controlled delivery of ramipril. Int. J. Drug Deliv. 5, 43–55.

Xu, H., Shi, M., liu, Y., Jiang, J., Ma, T., 2014. A Novel In Situ Gel Formulation of Ranitidine for Oral Sustained Delivery. Biomol. Ther. (Seoul). 22, 161–165. https://doi.org/10.4062/biomolther.2013.109