



RESEARCH PAPER

SUMATRIPTAN SUCCINATE LOADED MICROSPHERES CONTAINING COMPRESSED CORE TABLETS FOR EFFECTIVE TREATMENT OF MIGRAINE

Vinita Chaurasia, Vikas Kumar and Dharmendra Jain*

Department of Pharmaceutical Sciences, Dr. H. S. Gour Central University, Sagar-470003, Madhya Pradesh, India

*E-mail: dharmjain@gmail.com
Tel.: +91 9425972368.

Received: Jun 06, 2016 / Revised: Aug 16, 2016 / Accepted: Aug 17, 2016

Migraine has long been regarded as a vascular disorder because of the throbbing nature of the pain. Most patients with migraine require pharmacologic treatment. In the present research work sumatriptan succinate is used in the form of compressed core tablets *via* oral route of administration for effective treatment of migraine. The aim of this study was to reduce the dosing frequency and avoid hepatic first pass metabolism by preparing sumatriptan succinate loaded alginate microsphere. The microspheres were prepared by emulsification method. The prepared microsphere were characterized by scanning electron microscopy, and evaluated for different parameters like particle size, entrapment efficiency, polydispersity index, surface charge and *in vitro* drug release. The microsphere loaded compressed core tablets were prepared by direct compression method, where the drug loaded microsphere was present in the core of tablet. Further the outer coating layer was applied on the core of tablet that contains plain sumatriptan succinate to immediate release and provides instant relief from migraine symptoms. The formulations were evaluated for various parameters as well as *in vitro* drug release and compared with plain sumatriptan succinate loaded compressed core tablet. The *in vitro* drug release showed immediate drug release within 2 min from outer coating layer as well as sustained drug release for up to 24 h from core of tablet. It is concluded that the formulation provide instant as well as delayed release of drug to migraine patient which can decrease the dosing frequency and increase patient compliance.

Key words: Migraine, Sumatriptan succinate, Core tablet, Microsphere, Orodispersible layer.

INTRODUCTION

Migraine is a complex neurobiological disorder that has been recognized since antiquity. The core features of migraine are headache, which is usually throbbing and often unilateral, and associated features of nausea, sensitivity to light, sound, and exacerbation with head movement (Silberstein *et al* 2002). Headache is one of the most common medical complaints in migraine. Preventive treatments for patients with migraine headache, reduce the frequency, severity, and duration of headaches (Rubingh *et al* 2007). The

pain of migraine headaches usually begins gradually and intensifies over a period of minutes to hours and can be aggravated by light or sound, constant motion, or any physical activity. These headaches usually last from 4 to 48 h and can be relatively mild to severe (Russo, 1998). Symptoms that accompany the intense headache such as blurred vision or blind spots, sweating, runny or blocked nose, fatigue, nausea and vomiting, loss of appetite, numbness, tingling, problems in concentrating, sensitivity to light, sound, or smells etc (Villalon *et al* 2002).

Symptoms may continue even after the migraine has gone away; this is sometimes called migraine hangover, where the patient feels mentally dull with unclear thinking, has an increased need for sleep, and sometimes experiences neck pain (Dahlof, 2005). Five phases can often be identified: Prodrome (warnings before a migraine like changes in mood), Aura (visual or other sensory disturbance), Headache (pain), Headache termination (pain usually goes away with sleep), and Postdrome (other signs of the migraine like inability to eat or fatigue etc.) (www.emedicinehealth.com).

Pathophysiology of migraine

The exact pathophysiology of migraine is unknown. The prevailing theory is that a trigger (such as fatigue, stress, or certain foods) sets off a wave of brief neuronal activation, followed by a more sustained neuronal inhibition known as Cortical Spreading Depression (CSD) (<http://www.headache-treatment.com>).

The exact mechanism responsible for the disorder is not known, but the head pain is related to dilatation of extra cranial blood vessels, which may be the result of chemical changes that cause spasms of intracranial vessels. The prodromes are thought to be related to constriction of the arterioles (Terry *et al* 1993). This neurovascular disorder related to dysfunctions in brainstem centers which regulate vascular tone and pain sensation. In the pathophysiology of migraine, both central and peripheral mechanism, as well as nerves and vessels are involved (Listos *et al* 2013).

Medication therapies

Medication therapies are categorized into acute, preventive and rescue. Almost all migraineurs require acute therapy and a rescue treatment for when routine therapy fails. A smaller group of patients (up to 40%) may need daily preventive therapy (Dandge *et al* 2009). This is usually reserved for those who experience frequent attacks (*e.g.* three to six or more attacks per month), a substantial number of headache days (more than 6-8 days per month) and/or have poor response to or intolerable adverse events from acute care medication (Evers *et al* 2009). Non pharmacological treatments, such as biofeedback therapy, relaxation techniques, cognitive restructuring and other behavioural therapies and acupuncture are generally categorized as preventive treatments as they may help reduce the frequency and severity of

attacks. Pharmacological therapies may be used in conjunction with acute and preventive medication treatments (Rapoport *et al* 2010). Two pharmacological treatment options exist for migraine: preventive and symptomatic treatment. Preventive treatment includes propranolol, amitriptyline, flunarizine, methysergide etc. Symptomatic or acute treatment is necessary for all patients with migraine. The symptomatic treatment options include simple analgesics, NSAIDs, antiemetics, ergot alkaloids, selective 5-HT receptor agonists etc (Tripathi, 2009; Rapoport *et al* 2010). These drugs may be used alone or in combination of two or more categories of medicament for better treatment of migraine. Relpax (Eletriptan hydrobromide), Imitrex (Sumatriptan succinate), Maxalt® (Rizatriptan benzoate) are some marketed product by Pfizer, GlaxoSmithKline, and Merck & Co. respectively for the treatment of migraine (www.drugs.com).

In the present research work a selective 5-HT receptor agonist sumatriptan succinate (**Figure 1**) is used for effective treatment of migraine via oral route of administration. Various drug delivery systems have been previously employed for delivery of sumatriptan succinate to migraineurs such as tablet, subcutaneous injections and nasal spray (Dandge *et al* 2009). Sumatriptan succinate is rapidly absorbed by subcutaneous injection, but the invasiveness and discomfort of the delivery, limits its use for many patients.

Drug delivery through nasal mucosa (nasal spray) also provides relief but chances of drug loss are more. Transdermal delivery of sumatriptan succinate also employed alone and or combination with naproxen (Khoury and Couch, 2010; Vikelis *et al* 2012). Oral bioavailability of sumatriptan succinate is very less due to high first pass metabolism and short half life.

In acute migraine patients, there is a need of repeating the dose every 2-3 h after initial dose. Hence, patients have to take medication repetitively. The main aim of this study to overcome this problem, by preparing compressed core tablets and were assumed to release drug after 2-3 h of initial dose and maintains it for longer period of time. Microspheres are one of the widely acceptable multiparticulate drug delivery systems and past literature reports formulation development of microspheres of many drugs (Dahiya and Tyagi, 2008; Kumar and Dureja, 2011; Tripathi *et al*

2011; Dahiya and Gupta, 2011; Basarkar *et al* 2013; Verma *et al* 2014). Here, in the formulation of compressed core tablets, core tablets will contain either plain drug or drug loaded microspheres. The core tablets will be either non-coated or enteric coated. Core tablets containing drug loaded microspheres will be prepared to further prolong the drug release from the formulation, so that patient needs not to take medicine again and again. Then, core tablets will be coated with orodispersible powder (as outer coating layer) by compression coating. This faster dissolving outer coating will provide immediate relief from migraine symptoms, while inner core will release drug after some time delay. The main objective of the present work is to increase patient compliance by providing instant relief and decreasing dosing frequency by sustaining the release of drug for longer period of time.

MATERIALS AND METHODS

Materials

Sumatriptan succinate was given as gift sample from Sun Pharmaceuticals Pvt. Ltd. Vadodara, India, Sodium alginate, calcium chloride, magnesium stearate were purchased from Central Drug House (P) Ltd, New Delhi, India, Hydroxypropyl Methylcellulose (E5, E15), Dibasic calcium phosphate, talc were obtained from Loba Chemie, Mumbai, India, Sodium saccharine, polyvinylpyrrolidone (PVP) were purchased from Himedia laboratory, Mumbai, India. Distilled water was used as solvent if not otherwise stated. All other reagents used were of analytical grade.

Methods

Drug excipient compatibility study

Drug excipient compatibility study was performed using FTIR spectroscopy. In this pure sample of sumatriptan succinate alone and in the formulation was observed under FTIR spectroscopy. Any change in the standard peak of drug's functional groups may be regarded as

change in the drug characteristics on addition of excipients thus considered as incompatibility between drug and excipients.

Formulation of compressed core tablets

The whole method for the preparation of compressed core tablets can be divided into the following 5 steps described below:

Preparation of sumatriptan succinate loaded alginate microspheres by emulsification method

The alginate microspheres were prepared by emulsification method (Rahman *et al* 2006). Briefly Sumatriptan succinate (400 mg) was dispersed in an aqueous solution of 5% w/v sodium alginate and this dispersion were emulsified in liquid paraffin containing 2% v/v span 80 using a mechanical stirrer (Remi Instruments Ltd, Mumbai, India) at 1500-2000 rpm for 1 h. Calcium chloride solution (5% w/v in isopropanol) was added to the emulsion at the rate of 2 ml/min. The emulsion was stirred for 10 more minutes. The prepared microspheres were collected by filtration and washed 3 times with cyclohexane to remove liquid paraffin. Microspheres were deep frozen at -70°C for 12 h. Then, the frozen microspheres were lyophilized for 8 h. and stored in air tight glass container until used.

Formulation of core tablets containing plain/microspheres loaded sumatriptan succinate by direct compression method

Core tablets of sumatriptan succinate were prepared by direct compression method and the formula is shown in **Table 1**. Briefly, the drug, polymer and diluents were weighed, sieved using mesh #40 and mixed thoroughly for 10 min. Then the lubricant talc and antiadherent magnesium stearate was added and the blend was again mixed well for another 5 min and then the powdered blend was compressed on a single station tablet punching machine using a 5 mm flat punch. For preparation of microspheres containing core tablets, weighed quantities of

Table 1. Formula of core tablets

Ingredients	Quantity (mg/tablet)
Sumatriptan succinate/Sumatriptan succinate loaded microspheres	80/279
Hydroxypropyl methylcellulose	80
Dibasic calcium phosphate	90
Polyvinylpyrrolidone	24
Magnesium stearate	2
Talc	3

microspheres (279 mg/tablet) were punched on rotary tablet machine in the similar manner described above. The amount of microspheres was calculated on the basis of drug entrapment efficiency in order to achieve similar weight of the drug in the tablet as that of plain drug containing tablets.

Enteric coating of core tablets

Core tablets (whether plain drug containing or drug loaded microspheres containing) were coated by the enteric coating solution by dip coating method. After coating once, the tablets were allowed to dry completely then coated again for one more time. The formula for preparation of enteric coating solution is given in **Table 2**.

Preparation of granules for orodispersible coating layer

Granules formulating orodispersible layer were prepared by wet granulation method. Briefly, drug (sumatriptan succinate), sodium starch glycolate (superdisintegrant), mannitol (diluent) were passed through mesh #40.

Then, wet mass was prepared by adding polyvinyl pyrrolidone which was dissolved in ethyl alcohol. The wet mass was passed through

mesh #16, formed granules were dried in an oven at 40°C for 4-5 h, and again passed through mesh #20.

Later, talc, sodium saccharine and magnesium stearate as required were incorporated and blended for 5 min. The granules were evaluated for bulk density, tapped density, angle of repose, hausner's ratio and carr's index and used for compression coating of sumatriptan succinate core tablets (either non-coated or enteric coated) (Kumar *et al* 2011). The formula of preparation of orodispersible granules is given in **Table 3**.

Compression coating of all types (non-coated or enteric coated) of core tablets using orodispersible granules

Procedure employed in the compression coating of core tablets is described (Lopes *et al* 2007). Briefly, half of the weight of coating granules (100 mg) was manually filled in the die cavity to make a coating bed. After filling of coating granules, the non-coated/enteric coated core tablets were placed in centre of the coating bed then the other half of the coating granules (100 mg) were added over the core tablet. The total mass was finally compressed to form compressed core tablet.

Table 2. Formula of enteric coating solution

Ingredients	Quantity taken
Cellulose acetate phthalate	3 g
Propylene glycol	1 ml
Acetone	20 ml
Isopropyl alcohol	30 ml

Table 3. Formula of orodispersible granules

Ingredients	Quantity taken (mg/tablet)
Sumatriptan succinate	20
Mannitol	142
Sodium starch glycolate	30
Poly vinyl pyrrolidone	2
Sodium saccharin	6
Talc	4
Magnesium stearate	2
Ethyl alcohol	q.s.

In this way, total four types of compressed core tablet were prepared:

- (i) Compressed core tablet of plain drug loaded non-coated core
- (ii) Compressed core tablet of drug loaded microspheres containing non-coated core
- (iii) Compressed core tablet of plain drug loaded

enteric coated core

- (iv) Compressed core tablet of drug loaded microspheres containing enteric coated core

The schematic of the steps involved in the preparation of compressed core tablets is presented in **Figure 1**.

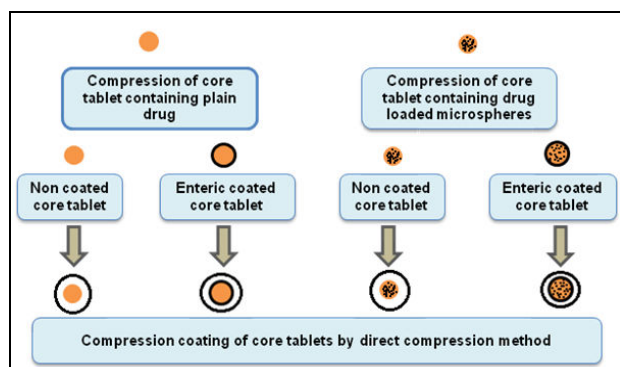


Fig. 1. Schematic of the steps involved in compressed core tablets

Characterization

Characterization of microspheres

Surface morphology and particle size determination

The surface morphology of sumatriptan succinate loaded microspheres was studied in Diya laboratory, Mumbai using scanning electron microscopy (SEM), (FEI Quanta 200 scanning electron microscope USA). The dried samples were mounted on brass specimen studies, using double sided adhesive tape. Gold-palladium alloy of 120°A knees was coated on the sample using sputter coating unit in Argon at ambient of 8-10 Pascal with plasma voltage about 20 MA. The sputtering was done for nearly 5 min. The SEM was operated at low accelerating voltage of about 10 KV. Particle size of microsphere was determined using Delsa Nano C Beckman coulter counter, Banaras Hindu University, Varanasi. The samples of prepared microspheres were diluted with deionized water. The particles size and size distribution were represented as average diameter.

Polydispersity index

Polydispersity indicated the degree of nonuniformity of the particle size (Jain and Banerjee, 2008). Polydispersity index of the microsphere was determined using Delsa Nano C Beckman coulter counter, Banaras Hindu University, Varanasi.

Surface charge or zeta potential measurement

The surface charge of microspheres was determined by measurement of zeta potential (ϵ) of the microspheres using Zetasizer Delsa nano C beckman coulter counter. The field strength was 20 V/cm on a large bore measures cell. Microspheres were diluted with double distilled water adjusted to a conductivity of 50 μ S/cm with a solution of 0.9% NaCl.

Drug entrapment efficiency

The prepared microspheres were filtered and collected, by draining the supernatant from the centrifuged tubes. 1 ml of supernatant was taken out in a 10 ml volumetric flask and made up the volume. 1ml again had taken out and further diluted upto 10 ml in a volumetric flask. Then the sample was filtered using a filter paper and absorbance was noted at 227 nm using UV spectrophotometer (Mini UV 1240, Shimadzu, Japan).

$$\text{Entrapment efficiency (\%)} = \frac{\text{Total amount of drug} - \text{Amount of drug lost}}{\text{Total amount of drug added}} \times 100$$

In vitro drug release study of microspheres

The drug release of sumatriptan succinate loaded microspheres was performed in PBS (pH 6.8) in USP XXIII (EI tablet dissolution test apparatus, India) in triplicate. 10 mg microspheres were taken into a dialysis bag and placed in USP apparatus containing 900 ml of PBS (pH 6.8) at 100 rpm for 12 hours. 1ml sample was withdrawn after one hour interval and replaced with the same volume of fresh PBS (pH 6.8). Then the withdrawn sample was diluted upto 10ml and analyzed using UV spectrophotometer at 227 nm.

Characterization of tablets

Weight variation

Twenty tablets from each formulation were selected randomly and weighed individually and average weight was taken to check for weight variation (Bandari *et al* 2008; Kannuri *et al* 2011).

Thickness

The thickness of individual tablet was measured by using vernier calliper, which permits accurate measurements and provides information on the variation between tablets (Rao *et al* 2012).

Hardness

The resistance of the tablet to chipping, abrasion or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of the tablets was determined using EI Monsanto Hardness tester (Bandari *et al* 2008).

Friability

It is the measurement of mechanical strength of tablets. Roche friabilator was used to determine the friability of the tablets. The tablets were

rotated in the friabilator for 4 minutes at 25 rpm dropping those tablets at a distance of 6 inches with each revolution (Parashar *et al* 2012; Samineni *et al* 2013; Mohammad *et al* 2014). The % friability was calculated using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity

The drug content of core and compressed core tablets was measured spectrophotometrically. For this purpose, 3 tablets were collectively weighed, and crushed. The weighed amount of powder containing equivalent to 80 mg (in case of core tablet) and 100 mg (in case of compressed core tablets) of sumatriptan succinate was suspended in 100 ml PBS (pH 6.8) and subjected to continuous stirring at 100 rpm. Then the sample was centrifuged at high speed and filtered using filter paper (Majeed and Khalil, 2014). Then, 1 ml was withdrawn and diluted up to 100 ml with PBS (pH 6.8) and analyzed at 227 nm against blank using UV spectrophotometer. The drug content was calculated using the following formula:

$$\text{Drug content (\%)} = (M_a / M_b) \times 100$$

Where, M_a is the drug content of the tablet, M_b is the total amount of drug.

Wetting time

Wetting time of the orodispersible tablet needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. In this test, 5 circular tissue papers of 10 cm diameter were placed in a Petri dish. Then, 10 ml of artificial salivary solution containing dye solution was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as the wetting time (Kela and Kesharwani, 2013; Patil *et al* 2014).

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and allowed it to wet completely (Sharma *et al* 2012). The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation:

$$R = 100 \times [(W_a - W_b) / W_b]$$

Dispersion time

In vitro dispersion time was measured by dropping a tablet in a 10 ml beaker containing 6 ml of artificial salivary solution (pH 6.8). Then the time required to completely disperse the tablet was noted (Nagar and Yadav, 2009).

Disintegration test

In vitro disintegration time of core and compressed core tablets were determined using disintegration test apparatus. The test was carried out on 6 tablets using the apparatus specified in IP 1996 in 0.1 N HCl for 2 h and then medium was replaced with phosphate buffer (pH 6.8) and maintained at $37 \pm 2^\circ\text{C}$ and the time was recorded for complete disintegration of the tablet (Parashar *et al* 2012).

In vitro drug release study

In vitro drug release studies of core (non-coated and enteric coated) tablets and compressed core tablets were carried out using USP paddle method specified in USP XXIII (EI tablet dissolution test apparatus, India) (Apparatus 2, 50 rpm, $37 \pm 0.5^\circ\text{C}$) in different dissolution medium. The scheme of using simulated fluids of different pH was as follow:

- 1st to 5th min in salivary solution (pH 6.8)
- 1st to 2nd h in simulated gastric fluid (pH 1.2)
- 3rd to 6th h in simulated intestinal fluid (pH 6.8)

At the end of the specific time period 1 ml of the sample was taken out and replaced with fresh respective buffer. The withdrawn samples were analyzed for drug content using UV spectrophotometer at 227 nm (Farshid *et al* 2014).

Stability study

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity throughout the expiration dating period (Patel *et al* 2011). The tablets were packed in aluminium foil and stored in stability chamber (REMI Environmental Test Chamber, India) maintained at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for a period of 30 days as prescribed by ICH guidelines for accelerated studies. The tablets were analyzed for the drug content and hardness at two time intervals "i.e."

15, 30 days (Ponugoti and Gonugunta, 2014; Chaturvedi and Verma, 2011; Gandhi, 2012).

RESULTS AND DISCUSSION

Drug excipient compatibility study

FTIR spectrum of sumatriptan succinate and its formulation was recorded, and it was in accordance with the reported peaks (Figure 2a, 2b). The FTIR spectra of sumatriptan succinate comply with its chemical structure and shows peaks for principal groups. The structural assignments for the characteristics absorption bands were found at 3374 cm^{-1} , 1708 cm^{-1} , 1565 cm^{-1} , 1339 cm^{-1} , 964 cm^{-1} for N-H stretching, C=O stretching, C=C aromatic stretching, C-N stretching, C-O stretching.

In the spectra of formulation of drug and polymer, there was neither masking of any characteristic peak nor existence of additional peak was observed (Figure 2b). Thus, it can be concluded that drug was compatible with the polymers used in formulating the compressed core tablets.

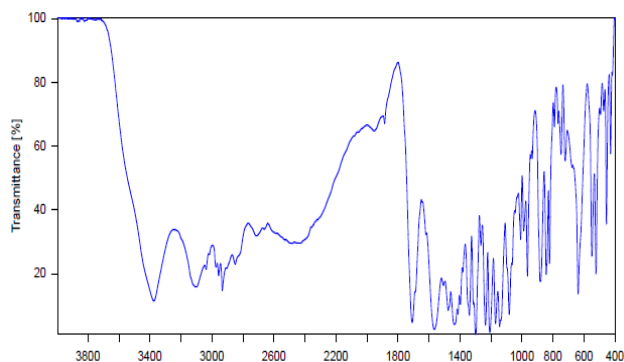


Fig. 2a. IR spectra of sumatriptan succinate

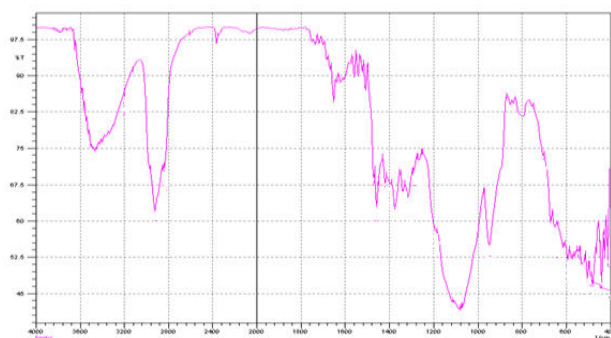


Fig. 2b. IR spectra of sumatriptan succinate with excipients in the formulation

Characterization of microspheres

Surface morphology and the particle size determination

The scanning electron microscopy (SEM), image of sumatriptan succinate loaded alginate

microspheres is shown in Figure 3. From the SEM image, it is clear that microspheres are of spherical in shape and having maximum particle size of almost 50 micrometer, which is well matching with the particle size obtained by Delsa Nano C Beckman coulter counter (Figure 4).

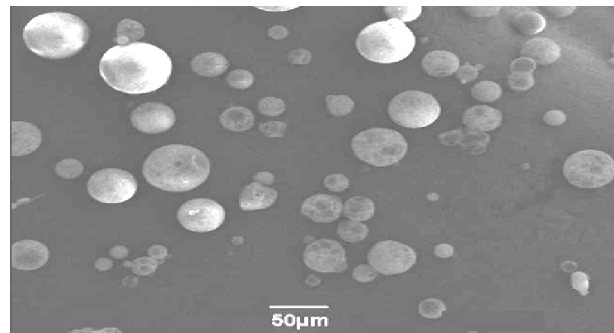


Fig. 3. SEM image of sumatriptan succinate microspheres

Similar particle size was observed on particle size determination of the microspheres diluted with deionized water using Delsa Nano C Beckman coulter counter. The particles size and size distribution were represented by average diameter (Figure 4, Table 4).

Polydispersity index (PDI)

Practically the value of PDI should be less than 0.5, as the value is more it shows a polydisperse system and if it is closer to zero, it denotes the monodisperse system. Polydisperse have greater tendency to aggregation than monodisperse system. The PDI value of the sumatriptan succinate loaded alginate microspheres was observed to be 0.196, indicating the uniformity and narrow size distribution of microspheres.

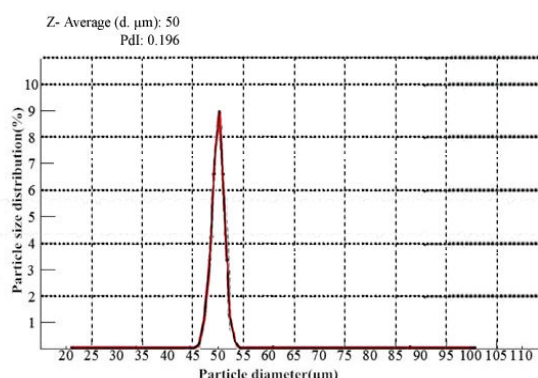


Fig. 4. Particle size and size distribution of the the microspheres

Surface charge or zeta potential measurement

The higher zeta potential of the alginate microspheres shows substantial electrokinetic

stability of the formulations. The average zeta potential of alginate microspheres were ranged ≈ -8.61 mV, showing that the microspheres are negatively charged. The results for average zeta potential analysis are presented in **Table 4**, **Figure 5**.

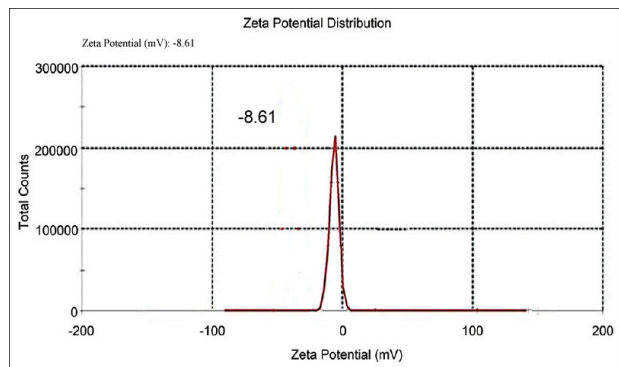


Fig. 5. Zeta potential of the microspheres

Table 4. Different parameters of sumatriptan succinate loaded alginate microspheres

Average particle size (μm)	Polydispersity index	Zeta potential (mV)
50	0.196	-8.61

Drug entrapment efficiency

Good entrapment efficiency of sumatriptan succinate was obtained in the alginate microspheres. The percent entrapment efficiency of sumatriptan succinate loaded microspheres was found to be 72.7%. This could be attributed to the hydrophilic nature of both the sumatriptan succinate and the microspheres forming polymer *i.e.* sodium alginate.

In vitro drug release study from microspheres

Sumatriptan succinate loaded sodium alginate microspheres were subjected to *in vitro* drug release studies in PBS (pH 6.8) using USP XXIII Type 2 dissolution apparatus. The average cumulative percent release profile of alginate microspheres at prefixed time intervals is presented in **Figure 6** as a function of time. Under the conditions used in the *in vitro* release studies, a biphasic pattern of drug release was observed. The release kinetics had two distinct phases: initially a faster release profile where almost 73 % drug was released within 8 h and thereafter sustained drug release till 12 h.

Characterization of compressed core tablets

The core tablets and compressed core tablets were characterized for the weight variation,

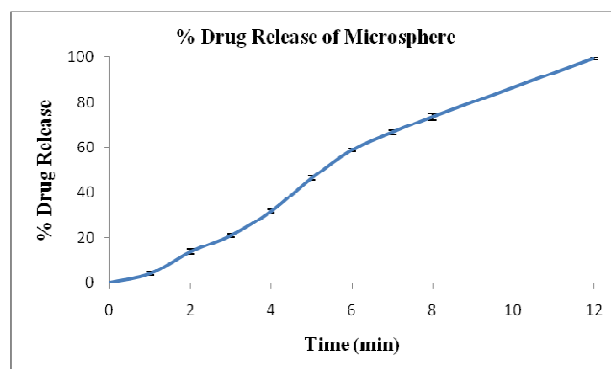


Fig. 6. *In vitro* drug release from alginate microspheres

thickness, hardness, friability, drug content uniformity, wetting time, water absorption ratio, dispersion time etc. The data obtained for these evaluation parameters is given in **Table 5a, b**.

In vitro drug release study from compressed core tablet

The developed formulations were subjected to *in vitro* drug release studies using USP XXIII Type 2 dissolution apparatus at different conditions. It was observed that core tablets C_1 and C_3 started drug release in the stomach while core tablets C_2 and C_4 protected the drug at stomach pH because of enteric coating and released drug in the small intestine.

Outer coating (orodispersible) layer of all the formulations showed the % drug release of range 99.01 ± 0.11 to 99.95 ± 0.12 within 2 min which fulfilled the requirement of addition of the coating layer by releasing maximum drug in minimum time in order to provide instant relief from migraine symptoms.

Formulation F_1 and F_3 showed drug release at stomach pH which was unsuitable, as the bioavailability of the sumatriptan succinate will not be enhanced. Formulation F_2 and F_4 released drug at intestinal pH and provided sustained release of the drug and hence, bioavailability will be increased. F_2 and F_4 released drug upto 7 h and 24 h respectively. It was observed that core tablet C_4 and formulation F_4 showed drug release for longer duration of time as they contained sumatriptan succinate loaded microspheres and release was observed upto 24 h (**Figure 7**).

In vitro drug release study of core tablets (C_1 - C_4)

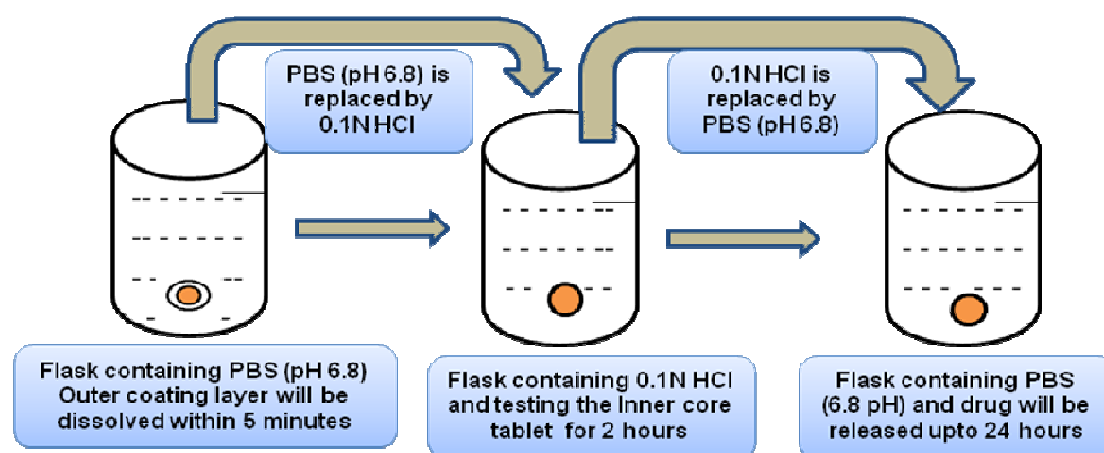
In vitro drug release of core tablets were carried out by using USP XXIII paddle apparatus (EI tablet dissolution test apparatus, India) at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. Release study was carried out in 0.1 N HCl (pH 1.2) for 2 h (average

Table 5a. Evaluation parameters of core and compressed core tablets (C₁-C₄)

Parameters	C ₁	C ₂	C ₃	C ₄
Weight variation ^a (mg)	0.270±0.0102	0.273±0.008	0.279±0.003	0.275±0.003
Thickness ^b (mm)	1.32±0.044	1.34±0.089	1.28±0.083	1.36±0.114
Hardness ^b (kg/cm ²)	5.45±0.58	5.50±0.45	5.34±0.42	5.54±0.55
Friability ^c (%)	0.78±0.63	0.22±0.36	0.51±0.45	0.35±0.52
Drug content ^d (%)	99.75±1.22	100.5±1.36	99.21±0.65	99.70±1.45
Wetting time ^d (min)	---	---	---	---
Water absorption ratio ^d (%)	---	---	---	---
Dispersion time ^d (min)	---	---	---	---

Table 5b. Evaluation parameters of core and compressed core tablets (F₁-F₄)

Parameters	F ₁	F ₂	F ₃	F ₄
Weight variation ^a (mg)	0.469±0.009	0.472±0.008	0.478±0.001	0.474±0.001
Thickness ^b (mm)	1.42±0.083	1.44±0.134	1.40±0.141	1.42±0.083
Hardness ^b (kg/cm ²)	5.21 ±0.24	5.42 ±0.22	5.12 ±0.26	5.43 ±0.38
Friability ^c (%)	0.38 ±0.21	0.46 ±0.25	0.45± 0.18	0.47± 0.29
Drug content ^d (%)	99.33±1.34	99.32±1.45	98.47±1.35	99.23±0.92
Wetting time ^d (min)	44 ± 1.35	45 ± 1.42	49 ± 1.49	51 ± 1.55
Water absorption ratio ^d (%)	0.51±0.45	0.56±0.46	0.65±1.21	0.55±0.36
Dispersion time ^d (min)	51±0.23	49±0.65	55±0.36	48±0.63

**Fig. 7.** Schematic of *in vitro* drug release study from compressed core tablets

stomach emptying time) to determine the difference in the efficiency of non-coated and enteric coated tablets. 1 ml of the sample was withdrawn at the end of 2 h. Then, the medium was replaced by PBS (pH 6.8). To determine the concentration of drug released, samples (1 ml) were withdrawn at prefixed time intervals and replaced by the same volume of PBS solution. Withdrawn sample was diluted upto 10 ml and

then analyzed using UV spectrophotometer at 227 nm (**Figure 8**).

In vitro drug release study of compressed core tablets (F₁-F₄)

In vitro dissolution study of compressed core tablets was carried out by using USP XXIII paddle apparatus (EI tablet dissolution test apparatus, India) at 37±0.5°C and 50 rpm.

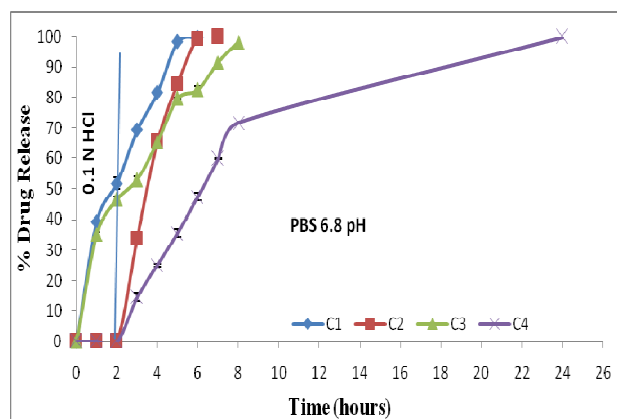


Fig. 8. *In vitro* drug release study from the core tablets

For first 2 min, the release study was carried out in PBS (pH 6.8) because the pH of saliva is 6.8. 1 ml of the sample was withdrawn at each minute. After 2 min, the dissolution medium was replaced by 0.1 N HCl (pH 1.2) for next 2 h, to

check the enteric coating, whether it remains intact or not in presence of HCl. 1 ml sample was again withdrawn at the end of 2nd hour. After completion of 2 h, again the dissolution medium was replaced by PBS (pH 6.8).

Then, 1 ml sample was withdrawn at the end of each hour till 24 h and 1 ml fresh medium was added each time. The samples were diluted upto 10 ml with PBS (pH 6.8) and analyzed using UV spectrophotometer at 227 nm. The *in vitro* drug release from compressed core tablets is shown in **Figure 9a, b**. F1, F2 and F3 showed complete drug release within 6-8 h, whereas sustained drug release was observed for 24 h from F4. Release from F2 and F4 was observed to be started delayed on changing the release media from PBS (pH 6.8) to 0.1 N HCl, The reason for which may be the presence of enteric coating on the core tablets (*i.e.* F2 and F4), which does not dissolve at acidic pH.

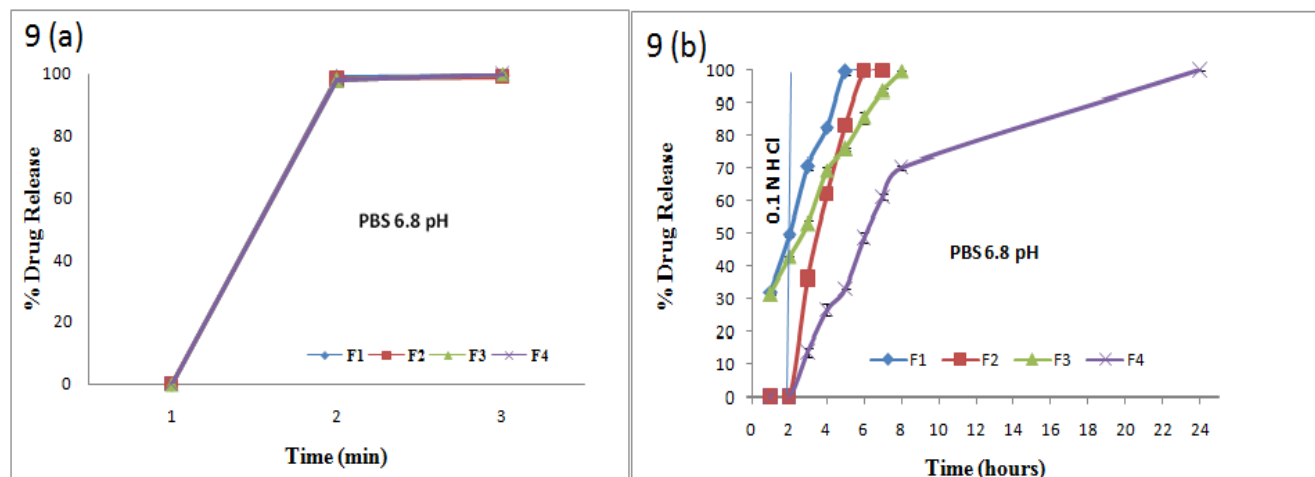


Fig. 9. *In vitro* drug release study from (a) outer coating layer (orodispersible) and (b) inner core of the formulations (*i.e.* F₁, F₂, F₃ and F₄)

Stability study

The formulations *i.e.* F₁, F₂, F₃ and F₄ were stored at 40±2°C and 75±5% RH. Change in residual drug content and hardness after storage for 0, 15, 30 days were determined.

It was observed that the % drug content was decreased from 99.33±1.34 to 98.78±1.12% (F₁), 99.32±1.45 to 99.05±0.45 (F₂), 98.47±1.35 to 98.09±1.03 (F₃) and 99.23±0.92 to 99.01±1.01 (F₄), and in case of hardness, it was decreased from 5.21±0.24 to 5.11±0.45 (F₁), 5.42±0.22 to 5.36±0.62 (F₂), 5.12±0.26 to 5.09±0.65 (F₃) and 5.43±0.38 to 5.3±0.12 (F₄). The results showed that there was no significant difference in both the drug content and hardness, indicating that the formulations were stable at the given environmental condition (**Table 6**).

SUMMARY AND CONCLUSIONS

Present work reports successful development of compressed tablets of sumatriptan succinate in order to overcome the disadvantages of its conventional oral drug delivery like loss of drug effects, less bioavailability, higher dosing frequency. This was attempted and achieved by formulating compressed core tablets where inner core tablet contained either plain drug or drug loaded microspheres and outer coating comprised of orodispersible layer which would provide immediate relief from migraine symptoms, while inner core would provide delayed drug release. To further delay the drug release, the core tablets were enteric coated, so that the release can be achieved once the tablet reaches to the intestine.

Table 6. Summary of results of stability studies

Parameters		F1	F2	F3	F4
Hardness (Kg/cm ²)	Initial	5.21 ± 0.24	5.42 ± 0.22	5.12 ± 0.26	5.43 ± 0.38
	15 days	5.20 ± 0.34	5.40 ± 0.36	5.11 ± 0.52	5.40 ± 0.31
	30 days	5.11 ± 0.45	5.36 ± 0.62	5.09 ± 0.65	5.3 ± 0.12
% Drug content	Initial	99.33±1.34	99.32±1.45	98.47±1.35	99.23±0.92
	15 days	99.12 ± 0.65	99.22 ± 1.36	98.40 ± 1.12	99.15 ± 0.96
	30 days	98.78 ± 1.12	99.05 ± 0.45	98.09 ± 1.03	99.01 ± 1.01

Overall study suggested that drug entrapped microspheres loaded enteric coated core containing compression coated tablets can be a good choice to achieve instant as well as delayed and sustained drug release for symptomatic treatment of migraine. Thus, the patients need not to administer medicine again and again. This

approach will not only decrease dosing frequency, but also minimize drug loss (as it does not dump whole dose at a time) and increase the drug efficacy and patient compliance.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

- Bandari S, Mittapalli RK, Gannu R, Rao YM. Orodispersible tablets: an overview. *Asian J. Pharm.* 2008;2:2-11.
- Basarkar GD, Shirsath GN, Patil SB. Development of microspheres containing diclofenac diethylamine as sustained release topical formulation. *Bull. Pharm. Res.* 2013;3(1):14-22.
- Chaturvedi AK, Verma A. Fast disintegrating tablet technology: newly prospects. *Int. J. Pharm. Sci. Res.* 2011; 2(12):3046-50. [DOI: 10.13040/IJPSR.0975-8232.2(12).3046-50]
- Dahiya S, Gupta ON. Formulation and *in vitro* evaluation of metoprolol tartrate microspheres. *Bull. Pharm. Res.* 2011; 1(1):31-9.
- Dahiya S, Tyagi L. Preparation and evaluation of oxytetracycline hydrochloride microbeads for delayed release. *Pak. J. Pharm. Sci.* 2008;21(2):103-8.
- Dahlof C. Update on sumatriptan: new progress in migraine treatment. *Therapy* 2005;2(3):349-356. [DOI: 10.2217/14750708.2.3.349]
- Dandge BH, Dehghan MHG, Gaikwad VM. Preparation and characterization of mucoadhesive microparticles of sumatriptan succinate for intranasal delivery. *J. Pharm. Res.* 2009;2(9):1536-1539.
- Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sandor PS. EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. *Eur. J. Neurol.* 2009; 16:968-981. [DOI: 10.1111/j.1468-1331.2009.02748.x]
- Farshid A, Rama B, Muralidharan G, Nargund LVG. Formulation and evaluation of orodispersible tablets of zolmitriptan. *Asian J. Pharm. Clin. Res.* 2014;7(1):127-134.
- Gandhi A. Mouth dissolving tablets: a new venture in modern formulation technology. *Pharma Innov.* 2012; 1(8):14-21.
- Jain D, Banerjee R. Comparison of Ciprofloxacin hydrochloride-loaded protein, lipid, and chitosan nanoparticles for drug delivery. *J. Biomed. Mater. Res. Part B Appl. Biomater.* 2008;86(1):105-112. [DOI: 10.1002/jbmb.30994]
- Kannuri R, Challa T, Chamarthi H. Taste masking and evaluation methods for orodispersible tablets. *Int. J. Pharm. Ind. Res.* 2011;1(3):200-10.
- Kela SP, Kesharwani D. Formulation, characterization and evaluation of taste masked rapid disintegrating tablet of ofloxacin by ion exchange resin technique. *Int. J. Pharm. Sci. Rev. Res.* 2013;21(2):246-53.
- Khoury CK, Couch JR. Sumatriptan-naproxen fixed combination for acute treatment of migraine: a critical appraisal. *Drug Des. Devel. Ther.* 2010;4:9-17.
- Kumar M, Dureja H. Development and characterization of factorially designed 5-fluorouracil microspheres. *Bull. Pharm. Res.* 2011;1(1):54-61.
- Kumar PR, Doddayya H, Reddy SR. Design and evaluation studies on novel floating tablets for peptic ulcer treatment. *J. Adv. Pharm. Edu. Res.* 2011;2:159-176.
- Listos J, Budzynska B, Orzelska J. New advances in pharmacotherapy of migraine. *J. Analg.* 2013;1(1):18-25.
- Lopes CM, Lobo JM, Pinto JF, Costa PC. Compressed matrix core tablet as a quick/slow dual-component delivery system containing Ibuprofen. *AAPS PharmSciTech* 2007;8(3):E76. [DOI: 10.1208/pt0803076]
- Majeed SM, Khalil YI. Formulation and evaluation of bilayer matrix tablets of amoxicillin and esomeprazole as an oral modified release dosage form for treatment of peptic ulcer. *Int. J. Pharm. Pharm. Sci.* 2014;6(3):134-42.
- Mohammad S, Mohammad S, Srinivas B, Begum A. Evaluation of tablets by friability apparatus. *Int. J. Res. Pharm. Chem.* 2014;4(4):837-40.
- Nagar M, Yadav AV. Cinnarizine orodispersible tablets: a chitosan based fast mouth dissolving technology. *Int. J. PharmTech Res.* 2009;1(4):1079-91.
- Parashar B, Yadav V, Maurya B, Sharma L. Fast dissolving tablet. *Int. J. Appl. Pharm.* 2012;4(2):17-22.
- Patel NJ, Lakshmi CSR, Patel HP, Akul S. Formulation and evaluation of oral dispersible tablets of cinnarizine using direct compression technique. *Int. J. Pharm. Sci. Res.* 2011; 2(4):961-7.
- Patil MR, Gujarathi NA, Rane BR. Formulation and evaluation of mouth dissolving tablet: review article. *Pharm. Sci. Monitor* 2014;5(2):7-20.
- Ponugoti RSR, Gonugunta CR. Formulation and evaluation of mouth dissolving tablets of tramadol hydrochloride. *Trop. J. Pharm. Res.* 2014;13(5):669-75.
- Rahman Z, Kohli K, Khar RK, Ali M, Charoo NA, Shamsher AAA. Characterization of 5-fluorouracil microspheres for colonic delivery. *AAPS PharmSciTech* 2006;7(2):113-121. [DOI: 10.1208/pt070247]

- Rao KS, Patil KG, Dattatreya BU, Patil PS, Biradar KV. Design and evaluation of orodispersible tablets of sumatriptan succinate. *RGUHS J. Pharm. Sci.* 2012;2(3):41-7. [DOI: 10.5530/rjps.2012.3.4]
- Rapoport AM, Freitag F, Pearlman SH. Innovative delivery systems for migraine: the clinical utility of a transdermal patch for the acute treatment of migraine. *CNS Drugs* 2010;24(11):929-40. [DOI: 10.2165/11317540-00000000-000000]
- Rubingh C. Preventive therapy for migraine headache. *Adv. Stud. Pharm.* 2007;4(1):15-20.
- Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. *Pain* 1998;76(1-2):3-8. [DOI: 10.1016/S0304-3959(98)0033-5]
- Samineni R, Ramakrishna G, Balaji M, Kondala Rao K. Formulation and evaluation of sumatriptan succinate mouth disintegrating tablets. *Am. J. Adv. Drug. Deliv.* 2013; 1(5):759-69.
- Sharma D, Kumar D, Singh M, Singh G, Rathore MS. Fast disintegrating tablets: a new era in novel drug delivery system and new market opportunities. *J. Drug Del. Ther.* 2012;2(3):74-86.
- Silberstein SD, Lipton RB, Goadsby PJ. Headache in Clinical Practice, 2nd edition, CRC Press: London, 2002; 797-804.
- Terry RS, Wernicke JF, Baker RG. Therapeutic treatment migraine symptoms by stimulation. US Patent 1993 [Patent number US 5215086 A].
- Tripathi KD. Essentials of Medical Pharmacology, 6th edition, Jaypee Brothers Medical Publishers(P) Ltd: New Delhi, 2009; 169-172.
- Tripathi M, Radhika PR, Sivakumar T. Formulation and evaluation of glipizide hollow microballoons for floating drug delivery. *Bull. Pharm. Res.* 2011;1(1):67-74.
- Vikelis M, Mitsikostas DD, Rapoport AM. Sumatriptan transdermal iontophoretic patch (NP101-Zelrix™): review of pharmacology, clinical efficacy, and safety in the acute treatment of migraine. *Neuropsychiatr. Dis. Treat.* 2012;8:429-434. [DOI: 10.2147/NDT.S27456]
- Villalon CM, Centurion D, Valdivia LF, De Vries P, Saxena PR. An introduction to migraine: from ancient treatment to functional pharmacology and antimigraine therapy. *Proc. West. Pharmacol. Soc.* 2002;45:199-210.
- Verma S, Kumar V, Jyoti, Mishra DN. Formulation, evaluation and optimization of mucoadhesive microspheres of acyclovir. *Bull. Pharm. Res.* 2014;4(1):14-20.
