INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION AND EVALUATION OF RANITIDINE SEMISOLID MATRIX CAPSULE BY LIQUID FILLING TECHNOLOGY

Kadam Sagar[*1], Dr. Kshirsagar Sandip[2], Shinde Vaishali[2]

[1]*Hon.Shri. Babanrao Pachpute Vichardhara Trust's, Group of Institutions, College of Pharmacy, Kashti, Ahmednagar, Maharashtra, India*

[2]*Kasturi Shikshan Sanstha, College of Pharmacy, Shikrapur, Pune, Maharashtra, India.*

ARTICLE INFO

Article history
Received 28/06/2019
Available online
31/07/2019

Keywords
Liquid Filling,
Capsule,
Ranitidine,
Matrix Tablet.

ABSTRACT

The aim of the present study was formulation and development of Ranitidine capsules by liquid filling technology in order to improve its dissolution properties and thereby its bioavailability. Ranitidine falls under histamine H2-receptor antagonist, a drug used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. Antagonists at Histamine H2-receptor are used in the treatment of dyspepsia; however their use has waned since the advent of the more effective proton pump inhibitors. Similar to the H1-antihistamines, the H2 antagonists are inverse agonists rather than true receptor antagonists. Excipients like polyethylene glycol 400 (PEG 400), propylene glycol (PG), polyvinylpyrrolidone (PVP K-30), antioxidants, ethanol, and purified water were used for formulation. These prepared formulations were evaluated for appearance, pH, viscosity, drug content percentage, stability, and in vitro dissolution studies. The compatibility between the drug and excipients in formulations was confirmed by FTIR spectra. The drug contents were in the range of 99.62-99.63 and the viscosity was in the range of 60.9–591.7 cps with all the formulations developed.

Corresponding author
Kadam Sagar
Hon. Shri. Babanrao Pachpute Vichardhara Trust's,
Group of Institutions, College of Pharmacy,
Kashti-414701, Ahmednagar,
Maharashtra, India.
vsk.vision11@gmail.com
7304705252

*Please cite this article in press as **Kadam Sagar** et al. Formulation and Evaluation of Ranitidine Semisolid Matrix Capsule by Liquid Filling Technology. Indo American Journal of Pharmaceutical Research.2019:9(07).*

INTRODUCTION

Soft gelatin capsules are kind of formulations which are formed, filled and sealed in one continuous operation. Soft gels present several advantages like versatile size, shape and elegance, tamper proof, content uniformity etc. Several advantages of soft gelatin capsules derive from the fact that these contain the active ingredient in solution, suspension or emulsion [1]. This will inherently lead to better absorption of the active ingredient as compared with delivery of a tablet or a powder and patients find it easier to swallow capsules than tablets. This preference has promoted pharmaceutical manufactures to market the product in capsule form .The present invention provides a new composition for treating pain associated sleep disturbances, especially shortened sleep duration, comprising Ibuprofen and diphenhydramine hydrochloride[2] .Soft gelatin capsules shell was prepared using gelatin and glycerin as plasticizer. Capsules fill solution was prepared by using antihistaminic drug Ranitidine hydrochloride and excipients. The capsules were evaluated for their ability to release drugs within 60 minutes. Ranitidine hydrochloride is a histamine H2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease, and erosive esophagitis [3-5]. The present investigation was aimed at developing oral administrable soft gelatin capsule (semisolid filling) pharmaceutical formulations of Ranitidine with improved dissolution properties.

MATERIALS AND METHODS

Ranitidine procured from Thermocil Fine Chem Ltd. Pune, PVP K 30, Propylene Glycol, Butylated Hydroxy Toluene, Sodium Meta Bisulfite and ethanol was obtained from Thermocil fine chem. Ltd. All ingredients were analytical grade. Empty soft gelatin capsule shells obtained from ACG Associated capsules Pvt. Ltd. Mumbai.

Preparation of Capsules

Preparation of fill medicament

Calculated quantity of ethanol (filtered through #80 mesh filter during dispensing) was charged into a clean vessel and butylated Hydroxy toluene was added into the above vessel with continuous stirring until it dissolved. After dissolving above solution accurate quantity of Ranitidine API was added and stirred for 15 minutes. After stirring disperse the above mixture in medium chain triglyceride and stirred for 15 minutes. The fill was unloaded and taken for encapsulation. The following were the different formulations of the fill material prepared in order to arrive at the best semisolid fill solution of Ranitidine drug.

Table1: Formulae for Semisolid Filled Capsule of Ranitidine.

Ingredients (mg/cap)	F_1	F_2	F3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}
Ranitidine	40	40	40	40	40	40	40	40	40	40	40
PVP K 30 (Polyvinylpyrrolidone)	—	—	—	—	10	10	20	—	10	10	20
PEG 400	100	100	160	130	120	120	110	130	120	120	110
Propylene Glycol	40	20	—	10	10	10	10	10	10	10	10
Butylated Hydroxy Toluene	—	—	—	—	—	—	—	—	—	1.0	1.0
Sodium Meta Bisulfite	—	—	—	—	—	0.1	0.1	—	—	—	—
Water	20	40	—	20	20	20	20	—	—	—	—
Ethanol	—	—	—	—	—	—	—	20	20	20	20

Evaluation Parameters for Ranitidine Semisolid Filling Formulations

Ranitidine Semisolid filling formulations were evaluated for appearance, viscosity, pH, and drug content.

Appearance

Capsules which are produced on a small or a large scale should be uniform in appearance. Visual as well as electronic inspection should be undertaken to detect any flaws in the integrity and appearance of the capsule. Physical instability of the formulation is primarily established by gross changes in appearance, including hardening or softening, cracking, swelling, mottling, printing mistake or discoloration of the shell. Defective capsules should be rejected. Appearance is the most important characteristic features of Semisolid filling formulations. All developed formulations were evaluated for appearance.

pH

pH is one of the most important parameter involved in the Semisolid filling formulations. Soft gel formulation should have a pH range between 2.5 and 7.5 The developed Ranitidine Semisolid filling formulations were evaluated for pH by using pH meter and estimations were carried out in triplicate.

Drug Content

To achieve dose uniformity, uniform distribution of active ingredient is very important. 10 mg formulation was taken in a 10 mL volumetric flask and dissolved in 5 mL methanol and the volume was made up with the methanol resulting in 2 mg of Ranitidine per 10 mL solution. 1 mL of the above solution was suitably diluted with pH 6.8 phosphate buffer. Finally drug content was estimated using UV 3092, Lab India UV-visible spectrophotometer in triplicate.

Rheological Studies

The viscosity was measured using Brookfield DV-II + PRO viscometer. The formulation was taken into the cup of viscometer and measured using spindle CP52 at the rotation of 10–100 rpm. The viscosity measurements were made in triplicate using fresh samples each time.

Viscosity Determination

Viscosity of gel mass is another important parameter in manufacturing of soft gelatin capsules. The viscosity should be in the specified limits to ensure smooth running of gel mass on machine. Viscosity of gel mass was determined using rheometric scientific viscometer.

Disintegration Test

The USP disintegration apparatus (Lab India) consist of 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly. To check disintegration time, one capsule is placed in each tube and the basket rack is positioned in specified medium at 37±2ºC such that capsule remains 2.5 cm below the surface of the disintegration liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. To move the basket assembly containing the capsules up and down through distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute ,standard motor driven device is used. Operate the apparatus for the specified time equilibrates the dissolution medium to 37±0.5°C.

In Vitro Dissolution Studies

In-vitro dissolution studies were carried out using 1000 mL of pH 6.8 phosphate buffer as a dissolution medium using a USP type II paddle method dissolution apparatus LAB INDIA). A temperature of 37 ± 0.5 °C and a rotation speed of 50 and 100 rpm were maintained. Semisolid formulations were filled into soft capsule and dissolution studies were performed. As the capsule is likely to float in the dissolution medium, sinkers were used. Sampling was done by withdrawing 5 mL at predetermined time intervals over a period of 2 hrs and then replaced with the same volume of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 267 nm using UV-visible spectrophotometer. Dissolution experiments were conducted in triplicate.

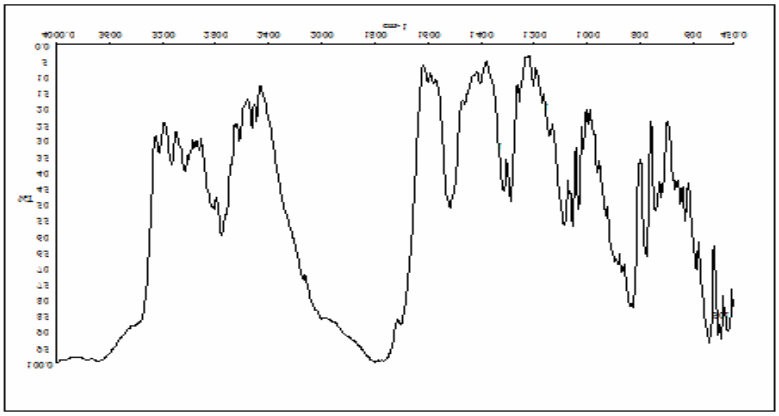
Stability Studies

Stability testing is done to ensure that drug products retain their fitness for use until the end of their expiration date. Formulations with Liquid filling (F4–F9) were observed for drug content, clarity, color change, and precipitation if any for a period of 3 months at room temperature (~30°C/65% RH).

RESULT AND DISCUSSION

FT-IR analysis

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000–500cm^{-1} at a resolution of 1.0 cm^{-1}. All samples formulations were simply placed onto the ATR crystal and each sample spectrum was collected. From the overlaid FT-IR spectra as shown in Figure1, it was confirmed that Ranitidine was compatible with different excipients used in the formulation.



(a)

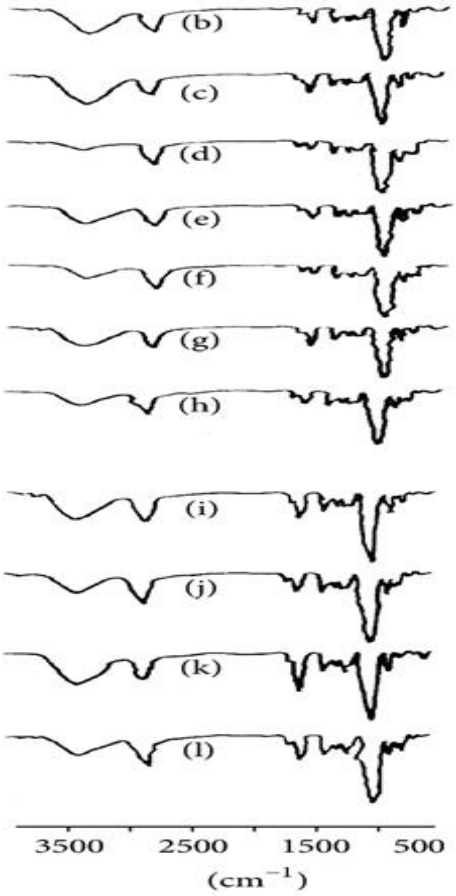


Figure 1: FT-IR spectra of (a)Ranitidine, (b)-F1, (c)-F2, (d)-F3, (e)-F4, (f)-F5, (g)-F6, (h)-F7, (i)-F8, (j)-F9, (k)-F10, and (l)-F11.

Appearance

The formulations (F1–F11) were homogeneous and colorless and no precipitation of drug was observed.

Table 2: Evaluation parameters for Ranitidine semisolid filling formulations (n=3).

Formulations	pH (mean ± SD)	Drug content (%) (mean ± SD)	Viscosity (cps) (mean ± SD)
F1	6.02 ± 0.21	98.63 ± 0.45	62.8 ± 0.10
F2	5.96 ± 0.15	98.94 ± 0.37	60.9 ± 0.02
F3	6.13 ± 0.15	99.10 ± 0.42	87.8 ± 0.06
F4	6.06 ± 0.15	99.26 ± 0.13	145.5 ± 0.10
F5	6.11 ± 0.17	99.63 ± 0.28	89.6 ± 0.01
F6	6.00 ± 0.17	99.76 ± 0.12	128.3 ± 0.05
F7	6.10 ± 0.20	99.56 ± 0.31	275.5 ± 0.01
F8	6.01 ± 0.14	99.34 ± 0.29	223.7 ± 0.07
F9	6.15 ± 0.20	99.61 ± 0.33	280.1 ± 0.01
F10	6.11 ± 0.13	99.17 ± 0.17	591.7 ± 0.03
F11	6.10 ± 0.17	98.62 ± 0.28	515.5 ± 0.02

pH

The pH of the formulations was about 6.0 and was within the limits. From Table 2 , it can be said that the pH of all liquid filling formulations was suitable for further studies.

Drug Content

The drug content found within the acceptable range for all formulations indicating uniform distribution of drug, that is, solubilization of Ranitidine in all the formulations. FromTable2, Ranitidine content was calculated for all the formulations prepared. Formulation F6 was found to be 99.76 % which was highest among all formulations.

Rheological Studies

Viscosity is one of the important parameters which provide vital information during the optimization of the semisolid filling formulation for soft gels. In general, the viscosity of semisolid filling formulations for soft gels is in the range of 0.222–3000 cps. From Table 2, it is observed that the viscosity of the formulations (without PVP) F1, F2, F3, F4, and F5 was low when compared to the formulations (with PVP) F6, F7, F8, and F9 based on their consistency. Formulations batches F1, F2, F3, F4, and F5 were fluid like consistency, whereas formulations F6, F7, F8, and F9 were slightly thick in consistency. The viscosity of formulations F10 and F11 were thicker in consistency and they failed to give viscosity at a higher shear rate (above 10 rpm). The consistency and viscosity of the filling formulations were related to each other because both were dependent on the concentration of PVP K 30. It was clearly evident that the viscosity and consistency of filling formulations were affected by concentrations of PVP K 30 and PEG 400.

Disintegration study of the capsules

Although there are official limits specified, ideally a disintegration time within 30 min as per BP is considered ideal for soft gelatin capsules. The formulated capsules disintegrated within a maximum of about 11 min as shown in the Table 3

Table 3: Disintegration Time of Capsules Formulation.

Formulation no.	Disintegration time (min)	
	Rupture time	Complete disintegration time
F1	7 min 44 sec	10 min 32 sec
F2	6 min 56 sec	11 min 18 sec
F3	7 min 13 sec	10 min 12 sec
F4	6 min 33 sec	10 min 47 sec
F5	6 min 23 sec	11 min 12 sec
F6	7 min 07 sec	11 min 48 sec
F7	6 min 12 sec	11 min 45 sec
F8	6 min 45 sec	11 min 14 sec
F9	7 min 15 sec	11 min 12 sec
F10	6 min 63 sec	11 min 23 sec
F11	7 min 25 sec	11 min 26 sec
Avg.	6 min 45 sec	11min 54 sec

In vitro dissolution studies

Totally 11 different filling formulations of Ranitidine were prepared with and without PVP K 30 and antioxidants. Dissolution profiles of the formulations demonstrated that Ranitidine dissolution was influenced by the solvents containing PVP K 30 rather than antioxidants incorporated in the formulation of the fill liquid. The control of the solvent system on Ranitidine dissolution was confirmed by comparing the percentage drug release at 10 min (DP_{10}) among the investigated formulae. All formulations exceeded 75% of Ranitidine released after 10 min, whereas only 25.4% was dissolved from the pure drug. Ranitidine dissolution from F1 was at the end of 10 min. This was due to the improper solubilization of Ranitidine in PEG 400 and PG. PG was decreased to 10% w/w in F2, resulted in of Ranitidine dissolution at the end of 10 min. This explained that PG in a lower concentration was suitable for dissolution. The effect of PEG 400 on dissolution was studied by preparing F3 without co solvents and showed of Ranitidine dissolution at the end of 10 min. In the subsequently step, PG as a co solvent at 5% w/w was incorporated in F4 and F5 for increasing the viscosity and thereby reduces the leakage. In F5, water was replaced with ethanol to evaluate the effect on Ranitidine dissolution. F4 and F5 showed and at the end of 10 min and these results indicated that the presence of ethanol in F5 significantly increased the dissolution of Ranitidine. The comparative dissolution profile for formulations F1, F2, F3, F4, and F5 was shown in Figure2.and comparative dissolution profile for formulations F4, F6, F8, F10, was shown in figure 3.

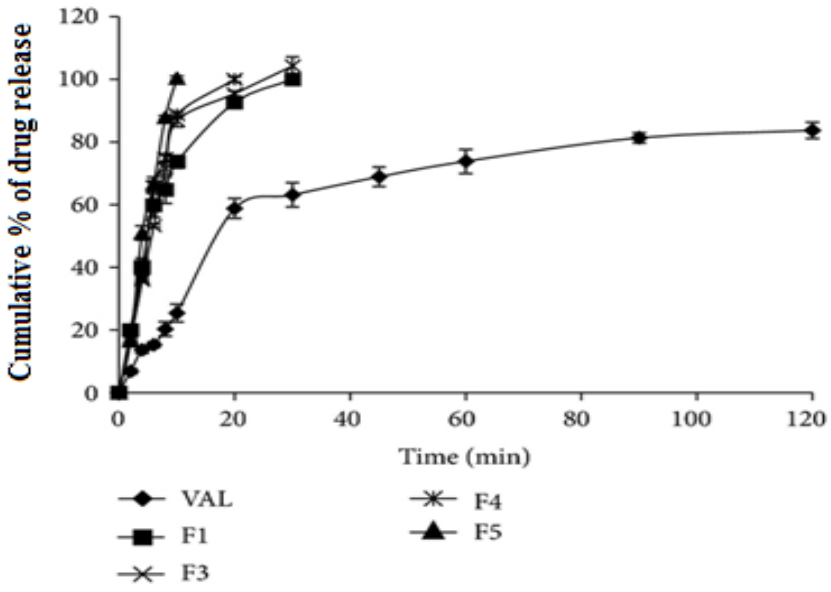


Figure 2: In Vitro Dissolution Profile for Ranitidine And Its Formulations F1, F2, F3, F4, AND F5 (n=3).

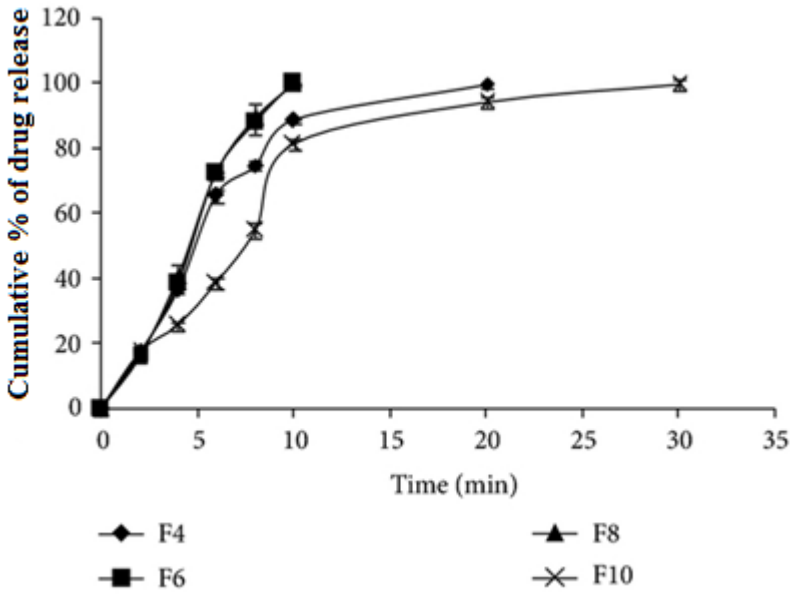


Figure 3: In Vitro Dissolution Profile for Formulations F4, F6, F8, And F10 (N=3).

Stability Studies

The formulations showed no changes in color and precipitation at the end of 3 months. The percent Ranitidine contents were also within the limits and the stability data was given in Table and shown in Figures 4.

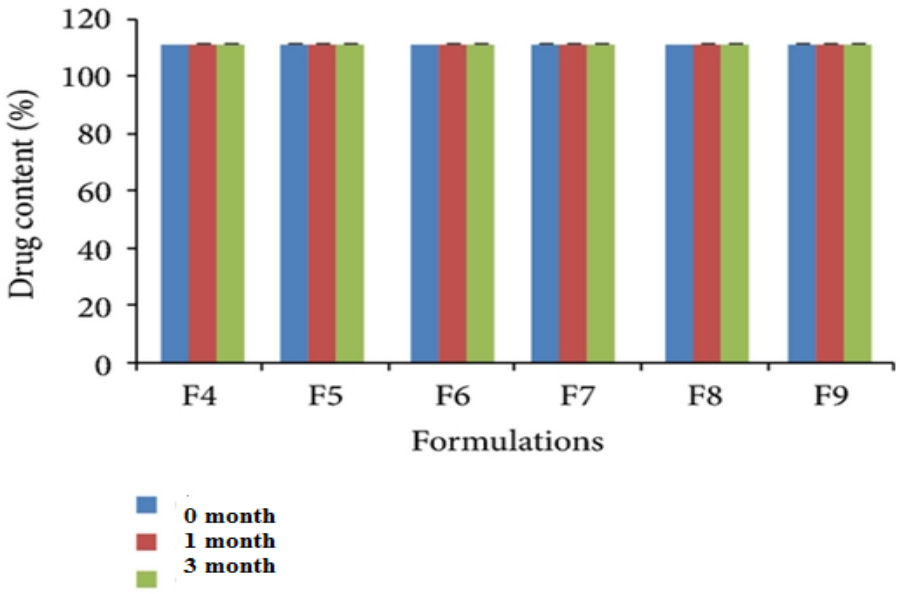


Figure 4: Stability Studies Data on PH, Viscosity, And Drug Content of Ranitidine Semisolid Filling Formulations F4–F9 (N=3).

CONCLUSION

The present investigation includes the preparation of semisolid filling formulations for soft gels using an histamine H2-receptor antagonist drug, Ranitidine , in order to improve its dissolution properties and thereby its bioavailability. The technology potentially provides the industry with an in-house process to develop drugs which are poorly water soluble, have low melting points, are highly potent or low dosed or contain a critical stability issue, into bioavailable, stable and safe dosage forms. Excipients like polyethylene glycol 400 (PEG 400), propylene glycol (PG), Polyvinylpyrrolidone (PVP K-30), antioxidants, ethanol, and purified water were used for formulations and then these formulations were evaluated for appearance, pH, viscosity, stability, drug content percentage, and in vitro dissolution studies. The compatibility between the drug and excipients in formulations was confirmed by FTIR spectra. The drug contents were in the range of 99.62-99.63 and the viscosity was in the range of 60.9–591.7 cps with all the formulations developed. Formulations containing 10 mg PVP K 30 gave better dissolution properties when compared to formulations without PVP K 30, and complete drug dissolution was observed within 10 min and followed the First-order release kinetics. Stability studies were conducted for selected formulations (F4–F9) for a period of 3 months at room temperature (~30∘C/65% RH). From the studies, it can be concluded that Ranitidine semisolid Filling formulations for soft gels were successfully prepared with in vitro dissolution properties superior when compared to Ranitidine itself.

ACKNOWLEDGEMENTS

The Authors are grateful to Cipla Pvt. Ltd, Mumbai for providing the gift sample of Glimepiride and also to the Principal, Hon. Shri. Babanrao Pachpute Vichardhara Trust's, Group of Institutions, College of Pharmacy, Kashti, Ahmednagar, for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

The authors declared that they have no any conflict of interest.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

REFERENCES

1. Croome RJ. Acid and alkaline hydrolysis of gelatine. Journal of Applied Chemistry.1953; 3: 280–286.
2. Margareth RC, Marques AB, Coleb C, Dale Kruep D Vivian GrayE, MurachanianF, et al. Liquid filled gelatin capsules. Pharmacopeial Forum. 2009;35(4):1029-1038
3. Ikushima H, Kawaguchi, Nakano H, Kodaira, Igusa K, Tokorozawa, Bessho S. Stabilized soft gelatin capsules composition of 1 α- hydroxyl- vitamin D. United States patent 1979 14; 4: 164-569.
4. Stoopak SB, Caldwell W, Kornblum SS, Field S, Jacobs AL, Randolph. Soft gelatin capsule with a liquid ergot alkaloid center fill solution and method of preparation. United States patent 1982; 366-45.
5. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, Varghese Publishing, Mumbai, India; 1987.
6. Ojantakanen S, Marvola M, Hannula M, Klinge E. Bioavailability of Ibuprofen from hard gelatin capsules containing different viscosity grades of HPMC and SCMC. European Journal of Pharmaceutical Sciences 1993; 1(2): 109-114.
7. Takahashi M, Yuasa H, Kanaya Y, Uchiyama. Study on dissolution of soft gelatin capsules by the rotating dialysis cell (RDC) method.VI. Preparation and evaluation of Ibuprofen soft gelatin capsule. Chemical and Pharmaceutical Bulletin 1995; 43(8): 1398-1401.
8. Ansel HC, Popovich NG, Loyd AV. Pharmaceutical Dosage Forms & Drug Delivery System. Sixth Edition; 1995:155-225.
9. Amemiya T, Mizuno S, Yuasa H, Watanabede J. Emulsion type new vehicle for soft gelatin capsule available for preclinical and clinical trials: effects of PEG6000 and PVP K30 on physicochemical stability of new vehicle. Chemical and Pharmaceutical Bulletin 1999; 47(4): 492-497.
10. Galal S, Massik M, Abdallah O, Daabis N. Formulation of fast release Glibenclamide liquid and semisolid matrix filled capsules. Acta Pharmaceutica 2003; 53: 57-64.
11. Rawlins EA. Bentley's Textbook of Pharmaceutics, Eighth Edition 2004: 269-318.
12. Remington. The Science & Practice of Pharmacy; Volume 1; 21st Edition 2006; 889-950.
13. Kreutzwald P, Malinovskaja K, Veski P. Effects of diluents and disintegrants on the release of poorly soluble drugs from hard gelatin capsules. European Journal of Pharmaceutical Sciences 2007; 32(1): 49-50.
14. Gullapalli RP. Soft gelatin capsules (softgels). Journal of Pharmaceutical Sciences 2010; 99:4107–4148.
15. Ghirardi P, Catenazzo G, Mantero O, Merotti GC, Marzo A: Bioavailability of Digoxin in a New Soluble Pharmaceutical Formulation in Capsules. Journal of Pharmaceutical Sciences. 1977; (2): 267-269.
16. Yaping Chen, Yi Lu, Jie lai, Jing sun, Wei Wu. Enhanced bioavailability of the poorly water soluble drug fenofibrate by using liposomes containing bile salts. International Journal of Pharmaceutics July. 2009; 1(2):153-160.