Formulation and Evaluation of Gastro Retentive Microspheres of Verapamil

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Abstract

The present study involves preparation and evaluation of floating microsphere using Verapamil Hydrochloride as a model drug for prolongation of the gastric retention time. The microspheres were prepared by the solvent evaporation method using different polymers like Hydroxy propyl methyl cellulose, Ethyl cellulose and polyvinyl pyrollidine. The average diameter and surface morphology of the prepared microsphere were characterized by optical microscope and scanning electron microscopic methods respectively. In vitro drug release studies were performed and the drug release kinetics were evaluated using linear regression method. The objective of the present study was to develop floating microsphere of Verapamil Hydrochloride in order to achieve anextended retention in the upper gastrointestinal tract, which may result in enhanced absorption and there by improved bioavailability. The prepared microspheres were evaluated for particle size, in vitro release, and buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was investigated.

***Key Words**: Verapamil Hydrochloride, Floating Microsphere, Hydroxy Propyl Methyl Cellulose, Ethyl cellulose, polyvinyl pyrollidine , Gastric Retention Time.*

Introduction

Controlled Drug Delivery System provides drug release at a predetermined, predictable and controlled rate to achieve high therapeutic efficiency with minimal toxicity. Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents and oral drug delivery is by far the most preferable route of drug delivery because of low cost of therapy and ease of administration leads to high levels of patient compliance as well as the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes, consequently much effort has been put into development of strategies that could improve patient compliance through oral route[1].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract [2] Conventional oral dosage forms such as tablets, capsules etc provide specific drug concentration in systemic circulation without offering any control over drug delivery and also great fluctuations in plasma drug levels, by comparison oral controlled drug delivery systems provide a release profile predominantly controlled by the design of the system itself [2,3] . The release of active agents is, therefore, largely independent of external factors. For oral solid delivery systems, drug absorption is unsatisfactory and highly variable between the individuals. An important requisite for the successful performance of oral controlled release drug delivery system is that the drug should have good absorption throughout the gastrointestinal tract (GIT). The major problem is the

physiological variability such as gastrointestinal transit in addition to gastric retention time, as the later plays a dominating role in the overall transit of the dosage form[4]. Another problem associated with the performance of oral controlled release systems is that even though the slow release can be achieved, the drug released after passing the absorption site (upper position of small intestine) is not fully utilized; this is because the GRT of the delivery system is less than 12 hours. Therefore, it is not possible to deliver the drug for more than 12 hours through the oral route. This has prompted researchers to retain the drug delivery systems in the stomach for prolonged and predictable time, such a prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug[4,5]. Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability[1,4,6].

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region[7].

Verapamil Hydrochloride is a phenyl alkyl amine hydrophilic papaverine congener, it is a calcium channel blocker. The entry of calcium into cells is of fundamental importance for normal functioning of cardiovascular system. In the SA node and AVnode in heart, the slow depolarization observed is consequence of slow inward movement of calcium. Calcium channel blocker decreases the calcium entry into both voltage operated and receptor operated channels and inhibits the calcium mediated slow channel component of action potential (AP) in smooth cardiac muscle cell and causes peripheral vasodilation[8,9]. Verapamil Hydrochloride is Almost completely absorbed after oral administration but undergoes extensive first pass metbolism. The main metabolic reactions are N-dealkylation and O-demethylation. About 50% of dose is excreated in urine in 24 hoursand 16% of dose is eliminated in the faeces.The mean oral bioavailability of Hydrochloride ranges from 20 to 30 %. Verapamil Hydrochloride is highly bound to plasma protiens (90%).half life of is 1.5 to 5 hrs. Verapamil Hydrochloride is indicated in angina pectoris, hypertension, arrythmias, hypertropic cardiomyopathy[10]

The present work deals with the formulation and characterization of Gastroretentive microspheres microspheres of esomeprazole hydrochloride using ethyl cellulose, polyvinyl pyrrolidone K-90 (PVP K-90) and poly vinyl alcohol.

Material and Methods

Verapamil Hydrochloride was received as gift sample from Nicholas Piramal (India) Ltd. Hyderabad Mumbai, India. Hydroxy propyl methyl cellulose K100M, polyvinyl pyrrolidone K-90 (PVP K-90) and Ethyl cellulose was purchased from Central drug house Pvt. Ltd. Tween 80, Dichloromethane and Ethanol were purchased from E.Merk (India) Ltd, Mumbai.All other chemicals were used as analytical grade.

Formulation of Floating Microsphere

The drug and polymers with different proportions (1:1, 1:2, 1:3) were weighed & co-solved at room temperature in to a mixture of ethanol -DCM mixture (1:1 v/v) with vigorous agitation to form uniform drug-polymer dispersion.This was slowly poured in to the dispersion medium consisting of 250 ml of water containing 0.01% Tween 80 maintained at temperature 30-40oC. This system was stirred using an overhead propeller agitator at 500 rpm at room temperature

over a period of 2-3 hours, to ensure complete evaporation of the solvent. The microsphere were filtered through a whattmann filter paper no 2 washed thrice with n-hexane and air dried for 24 hours[11].

Table-1. Formulation and design of Verapamil floating microsphere

	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Verapamil (mg)	40	40	40	40	40	40	40	40	40
HPMC(mg)	40	80	120	-	-	-	-	-	-
EC(mg)	-	-	-	40	80	120	-	-	-
PVP(mg)	-	-	-	-	-	-	40	80	120
Drug:Polymer	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
DCM:Ethanol (ml)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Tween 80	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%

Flow Properties[11]:

Bulk density:

Apparent bulk density (ρb) was determined by pouring the mass in to a graduated cylinder.The bulk volume (Vb) density was calculated in g/cm3 by the formula,

$$\text{Bulk density}(\rho b) = M/Vb$$

Tapped Density:

The measuring cylinder containing known amount of blend was tapped for a fixed time. The minimum tapped volume (Vt) occupied in the cylinder and weight of the (M) mass was measured. The tapped density was calculated in g/ cm3 by the formula,

$$\text{Tapped density} = M/Vt$$

Compressibility Index:

The bulk density and tapped density was measured and compressibility index was calculated using the formula,

$$\text{Compressibility index}=(DT - DP)/DT \times 100$$

Hausner ratio:

Tapped density and bulk density were measured and the Hausner ratio was calculated using the formula,

$$\text{Hausner ratio}=\text{Tapped density}/\text{Bulk density}$$

Angle of repose

The angle of repose, q, of the microspheres, which measures resistance to particle flow, was determined by the fixed funnel method and calculated.

$$\text{Tan } q = S/D$$

Estimation of incorporation efficiency:

To determine the incorporation efficiency, known amount of drug loaded microspheres were washed with 10 ml of SGF containing 0.1% v/v Tween 80 to remove the surface- associated drug. The filtered microspheres were then digested in a small amount of dichloro methane, to

release the entrapped drug from the microspheres. The drug was then extracted into the buffer by making up the volume to 100ml with the SGF and keeping it overnight in a metabolic shaker with slight shaking. The solution was then filtered and the drug content analyzed spectrophotometrically[12].

Total incorporation efficiency =surface associated drug + entrapped drug

Buoyancy percentage:

Micro particles were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 mol- HCl containing 0.01% Tween 80.The medium was agitated and the settled portion of microspheres were recovered separately.The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres [11,13,14].

$$\%\text{Buoyancy} = \frac{\text{Microsphereremained floating} \times 100}{\text{Total mass of microspheres}}$$

***In vitro* Drug release study**

The United States Pharmacopoeia basket-type dissolution rate test apparatus was used for all the *in vitro* release studies. A weighed quantity of the microsphere was suspended in 900 ml of 0.1 mol Hcl of pH 1.2.The dissolution medium was stirred at 100 rpm and maintained at constant temperature (37±0.5 ^{o}C).At preset time intervals 5 ml aliquots were withdrawn and replaced by

an equal volume of fresh pre-warmed dissolution medium maintaining sink condition throughout the experiment. After suitable dilution, the samples were analyzed for drug quantification.

Results and discussion

Verapamil hydrochloride floating microsphere was prepared by solvent evaporation method. Nine formulations were prepared with three different polymers. Each was used as three different concentrations. Table 1 shows the experimental design and various independent variables like

polymer type and drug to polymer ratio which have been changed at different levels. Each of these variables significantly influenced the various physicochemical parameters of the microsphere. The flow properties of all the formulations were found out by measuring the angle of repose and compressibility index. The results are shown in Table 2. The values of angle of repose were between 180-350, which are within the normal acceptable range of 200-400.The

porous microspheres showed reasonably good flow potential. This is further substantiated by the values of compressibility index (I) which was in the range 12 to 18, indicating good flow characteristics of the microspheres. This is also implies that the microspheres are non-aggregated.

The Verapamil-HPMC K100M microspheres showed better compaction ability when compared with Verapamil -EC & Verapamil -PVP microspheres. The improved micrometric properties of the prepared microspheres when compared to that of the pure drug alone, suggest that they can be easily handled and filled in to a capsule. Therefore

capsule loaded with microspheres can be suggested as a floating micro particulate drug delivery system. More ever the soft gelatin capsules easily absorb water and disintegrate and do not hinder with the floating capability of the microspheres.

The cumulative percentage drug release after 12 hours was found to be 95.4%, 85.3%, 75.8% for the formulation F1 to F3, while formulations F4 to F6 showed a percentage drug release of 80.4%, 79.1% and 89.2 % after 12 hours and F7 to F9 was found to be 77.4%, 76.4% and 76.1%.The results were shown in the Table 3. Figure 1 shows the plots of cumulative percentage released as a function of time for the formulations F1 to F3.It indicates a period that the drug release is prolonged over a period of 12 hours in case of Verapamil -HPMC K100M. Thus the Verapamil - HPMC K100M microspheres appear to be more efficient in controlling the drug release till the 12^{th} hour. It was also observed that the drug release generally decreased as the polymer ratio increased. Verapamil is water soluble present in the amorphous form with in the formulations. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used. Figure 1 shows the plots of cumulative percentage drug release as a function of time for the formulation F4 to F6, while Figure 3 shows the plots of cumulative percentage drug release as a function of time for the formulation F7 to F9.

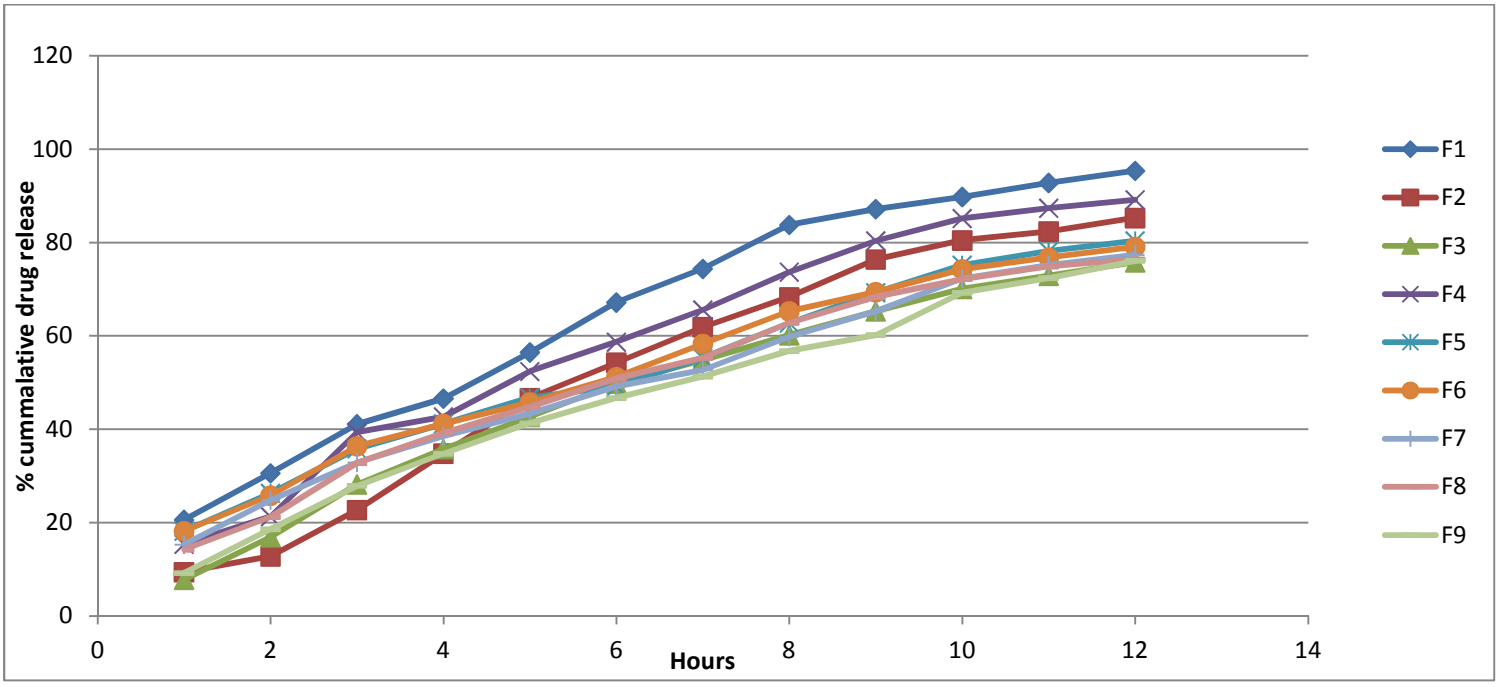
Table 2.Various parameters of characterization of the formulations

Batch code	Bulk Density	Tapped density	Angle of repose	Carr's Index (%)	Hausner's ratio
Pure drug	0.306	0.371	35°42'	17.52	1.213
F_1	0.621	0.712	23°32'	12.78	1.148
F_2	0.643	0.749	21°45'	14.15	1.164
F_3	0.656	0.785	18°76'	16.43	1.197
F_4	0.672	0.779	31°32'	13.73	1.160
F_5	0.701	0.812	30°46'	13.66	1.159
F_6	0.701	0.794	29°56'	12.84	1.148
F_7	0.683	0.792	30°62'	13.76	1.160
F_8	0.742	0.859	31°86'	13.62	1.159
F_9	0.698	0.801	30°56'	12.85	1.148

Conclusion

The present study an attempt has been made to formulate Verapamil hydrochloride into a micro particulate floating dosage form and prolong its gastric residence time, thus improving the oral bioavailability of the drug. It would be faster and more economical to alter beneficially the properties of the existing drugs than developing new drug entities. For the formulation, three biocompatible polymers, HPMCK100M, Ethyl cellulose and polyvinyl pyrollidine, were chosen in varying proportions with the drug. Solvent evaporation method was used to prepare porous microspheres employing dichloromethane and ethanol as solvents to dissolve the drug and the polymer.

Figure No:1:- % drug release of different formulation of esomeprazole



References

1. Chawla, G., Gupta, P., Koradia, V. and Bansal, A. K., Gastroretention- A means to address regional variability in intestinal drug absorption, Pharm.Tech., July 2003, 27(7): 50-51.
2. Chien Y.W., " Controlled and Modulated Release Drug Delivery Systems", in Encyclopedia of Pharmaceutical Technology, J. Swarbrick, J.C. Boylan, Eds., Marcel Dekker Inc., New York, 1990, pp. 280-285.
3. Jain, N.K., "Controlled Novel Drug Delivery", I[st] Eds., CBS Publishers and Distributors, New Delhi ,2002, pp.236-55.
4. Vyas, S.P. & Khar., " Targeted and Controlled Drug Delivery Novel Carrier System", I[st] Ed., CBS Publishers and Distributors, New Delhi, 2002, pp. 417-54.
5. Rezza, A., J. Microencapsulation, 1989, 6 (2): 219.
6. Garg, S. and Sharma, S., Gastro Retentive Drug Delivery Systems, Pharm. Tech., 2003,13(1):160.
7. P. Mojaverian, P. H. Vlasses, P. E. Kellner and M. . Rocci, "Effects of gender, posture and age on gastric residence time of an indigestible solid: pharmaceutical considerations", Pharm. Res., 1988, 10, 639–644
8. Gennaro, A. R., "Remington: The Science and Practice of Pharmacy", 1995,19th Edition,Mack Publishing Company,Eastern, Pennysylvania, pp.963.
9. Hardman, J.G., Limbird, L.E. in: Goodman and Gillman's, eds., " The Pharmacological Basis of Therapeutics", 2001, 10[th] Ed, Mac Grawhill, New York, pp.1791.
10. Reynolds, J.E.F., In: Martindale, The Extra Pharmacopoeia, 31[st] Edn., The Pharmaceutical Press, London, 1996,961-963
11. Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Itoh, Hollow microspheres for use as a floating controlled drug delivery system in the stomach, J. Pharm. Sci. 81 (1992) 135– 140.

12. Dhanaraju MD, Bhaskar K, Vamsadhara C. A multiple emulsion method to entrap hydrophilic compound into ethyl cellulose microspheres. *Indian Drugs.* 2003; 40(2): 99-103.
13. Srivastava AK, Ridhurkar DN. Floating microspheres of Cimetidine : formulation, characterization and in vivo evaluation, Acta Pharma. 2005; 55: 277-85.
14. Gohel MC, Mehta PR, Dave RK, Bariya NH. A more relevant dissolution method for evaluation of floating drug delivery systems, Dissolution technologies. 2004; 12: 22-25.