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Formulation and evaluation of Non Effervescent Floating Tablets of Verapamil Hydrochloride Using Peanut Husk Powder

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Abstract
In the recent years, scientific and technological advancements have been made in the research and development of novel drug delivery systems by overcoming physiological troubles such as short gastric residence times and unpredictable gastric emptying times. Gastric transit time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage form. Several approaches are currently utilized in the prolongation of the gastric residence times, including floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices[1]. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents ,the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration . in the present research we have studied pea nut husk powder as a floating agent.Floating tablets were prepared by direct compression method using verapamil and polymers Xantha gum and HPMC(grade K100M). Among three formulations FTV3 has shown a drug release of 75% after 8hrs and F2 has shown a floating lag time of 160sec.Based on invitro dissolution studies and floating studies ,increased concentration of peanut husk powder improves the floating nature but drug release is retarded due to increase in concentration of HPMC K100M.so present study concluded that the peanut husk powder can be used as an efficient floating agent.

Key words: *Gastric transit time, Floating drug delivery, Verapamil, Xantha gum, Pea nut husk powder and Floating lag time.*

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I. INTRODUCTION

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of flotation, mucoadhesion, sedimentation, expansion ,modified shape systems,or by the simultaneous administration of pharmacological agents that delay gastric emptying. Gastro retentive drug delivery systems can improve the controlled delivery of drugs that have an absorption window in the stomach by continuously releasing the drug for a prolonged period of time, thus ensuring its optimal bioavailability. Verapamil HCl is a calcium channel blocker used in the treatment of several cardiovascular disorders, particularly angina pectoris, supraventricular tachycardia and hypertension. It is established that 90% of verapamil HCl is absorbed following its oral administration and then it reaches maximum plasma concentration within 1-2hours. However, due to first pass effect it has low bioavailability (10-20%). It has a short half- life of 4 hours, so the dosing frequency is high. The physicochemical properties of Verapamil HCl and its short half life make it a suitable candidate for preparation of gastroretentive tablets.[2]

Non Effervescent floating drug delivery systems swell in gastric fluid and maintain a relative stability of shape and bulk density less than the density of the gastric fluid, which assists the floating process of these Dosage forms. However, effervescent floating drug delivery systems based on effervescent components will liberate carbon dioxide due to the acidity of the gastric fluid. Liberated gas bubbles will be entrapped in the gel layer formed by hydrocolloids that produce an upward motion of the dosage form and maintain its buoyancy.

Table 1: Materials

VERAPAMIL HCL	Yarrowchemproducts,mumbai
HPMC K_{100}M	Yarrowchemproducts,mumbai
XANTHAN GUM	Yarrowchemproducts,Mumbai
PEANUT HUSK POWDER	
MAGNESIUM STEARATE	Otto,chemical-biochemika-reagents
TALC	Qualikems

Verapamil[3]

Verapamil is widely used in the treatment of supraventricular tachyarrhythmias as well as for hypertension and control of symptoms in angina pectoris.. Plasma concentrations of verapamil appear to correlate with both electrophysiological and haemodynamic activity after either intravenous or oral drug administration, although considerable intra- and intersubject variation has been found in the intensity of pharmacological effects resulting at specific plasma drug levels. Verapamil is widely distributed throughout body tissues; animal studies suggest that drug distribution to target organs and tissues is different with parenteral administration from that found after oral administration. The drug is eliminated by hepatic metabolism, with excretion of inactive products in the urine and/or faeces. An N-demethylated metabolite, norverapamil, has been shown to have a fraction of the vasodilator effect of the parent compound in in vitro studies. The high hepatic extraction results in low systemic bioavailability (20%) after oral drug administration. Multicompartmental kinetics are observed after single doses; accumulation occurs during multiple-dose oral administration with an associated decrease in apparent oral clearance. Norverapamil plasma concentrations approximate those of verapamil following single or multiple oral doses of the parent drug.

Peanut husk[4]

Peanut husk powder is used as a natural polymer (cellulose35.7%, hemicelluloses 18.7%, lignin 30.2%) which is biodegradable, biocompatible, non toxic, economically cheap cost, devoid of adverse and side effects and easily available. It is a lightweight floating material. The seeds were dried in an oven at 40ºC for three hours and the surface layer was removed from the seeds by crushing them with hands. The husk was milled into fine powder by using a mixer grinder. The obtained Peanut Husk Powder (PHP) was passed through sieve100 and the fine powder was stored in a dessicator for further use.

II. PREPARATION OF PEANUT HUSK POWDER

- The seeds of peanut were collected from the market . These seeds were dried in the hot air oven at 40 degree centigrade for three hours and the surface layer was removed from the seed crushing them with hands . The husk was milled into fine powder by using a mixer grinder .
- Obtained peanut husk powder was passed through sieves no.100 and the fine powder was stored in a dessicator for further use.
- A fine and characteristic flavoured powder with light brown colour was obtained after milling the husk of peanut of plant ***Arachis hypogea* .** The peanut husk powder is a lightweight material with a bulk density of 0.54 g/ml as determined in our lab. The powder possesses fair flow property as it showed an angle of repose value of 34.88.

III. PREFORMULATION STUDIES :

3.1DETERMINATION OF MELTING POINT :

Melting point of verapamil HCL was determined by the capillary tube . The powder of verapamil HCL was filed in a glass capillary tube . The capillary tube is tied to the thermometer and the thermometer was placed on fire . the powder at what temperature it will melt was noticed.

3.2ANGLE OF REPOSE :

Angle of repose for different formulations was measured according to a fixed funnel standing method . The mixture was weighed and passed through the funnel , which was kept as a height “h” from the horizontal surface . The passed mixture forms a pile of the height “h” above the horizontal surface and that pile was measured and the angle of repose was determined for all the formulations using the formula .

$$\textbf{Angle of Repose} = \tan^{-1}(h/r)$$

3.3 BULK DENSITY AND TAPPED DENSITY:

Bulk density and tapped density were measured by using a 100 ml mixture in a cylinder . The sample poured into the cylinder was tapped mechanically for 100 times and then tapped volume was noted . Then bulk density and tapped density were calculated . Each experiment was performed in a triplicate manner.

The results of pre compressional parameters were given in table 2.

IV. CONSTRUCTION OF CALIBRATION CURVE :

4.1 PREPARATION OF 0.1N HCl:

Transfer 8.37 ml of concentrated HCl to 1000 ml volumetric flask and make up to 1000 ml with distilled water results in 0.1NHCl.

4.2 CALIBRATION CURVE oF VERAPAMIL HCL WITH 0.1N HCL:

An accurately weighed 25mg of Verapamil HCl was dissolved in 25ml of of 0.1N HCl in a volumetric flask (Stock solution I, 10µg/ml). From this solution 2.5ml was pipette out and the volume was made upto 25ml (Stock solution II, 1µg/ml). Then the aliquots were prepared by pipetting out 2,4,6,8,10 ml of stock solution II and 2,4,6,8,10 ml of stock solution I. Then the absorbance was measured at 278nm by using UV spectrophotometer.

V. PREPARATION OF SUSTAINED RELEASE FLOATING TABLETS OF VERPAMIL HYDROCHLORIDE:

The verapamil tablets were prepared by the direct compression method by incorporating the polymers like xanthan gum , hpmc , peanut husk powder , magnesium stearate and talc were included in the formulation as lubricating agents and glidant respectively.

Table2:Formulations of sustained release floating tablets of Verapamil Hydrochloride

INGRIDIENTS (API & EXCIPIENTS)	FTV1	FTV2	FTV3
VERAPAMIL HCL	40mg	40mg	40mg
HPMC $K_{100}M$	30mg	30mg	55mg
XANTHAN GUM	15mg	20mg	25mg
PEANUT HUSK POWDER	10mg	15mg	20mg
MAGNESIUM STEARATE	2.5mg	2.5mg	5mg
TALC	2.5mg	2.5mg	5mg

VI. PHYSICAL PROPERTIES OF TABLETS[5,6]

The prepared tablets were evaluated for weight variation ($n = 20$), hardness, friability ($n = 6$), and drug content as per IP 1996. Hardness of tablet was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test ($n = 20$) was conducted using Roche friabilator (F. Hoffmann-La Roche Ltd., Basel, Switzerland). The drug content of the manufactured tablets was estimated using UV spectrophotometric method. Floating tablet of verapamil hydrochloride from a batch was taken at random and was crushed to fine powder. The powdered material was transferred into a 100 ml volumetric flask and 70 ml of 0.1NHCl was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100 ml by adding0.1N HCl. About 10 ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using millipore filter. Then the filtrate was subsequently diluted and the absorbance was measured at 278 nm. This test was repeated six times (n = 6) for each batch of tablets.

6.4 IN-VITRO DRUG RELEASE STUDIES [7] :

- Dissolution apparatus: USP type II
- Dissolution Medium: 0.1N HCl
- Volume of dissolution medium: 900 ml
- Temperature: 37°C

- Speed of apparatus: 50 rpm
- Instrument: UV – spectrophotometer
- Wave Length: 278 nm

6.5 KINETIC MODELING :

The result of in vitro release data obtained for all formulations were fitted into four kinetic model of data treatment as follows :

Cumulative percentage drug released versus time(zero -order kinetic model)

Log cumulative percentage drug released versus time (first - order kinetic model)

Cumulative percentage drug released square root of time(higuchi's model)

Log cumulative %drug released versus log time(korsmeyer -peppas equation)

VII. RESULTS

The melting point was determined as 148^0c

Table3:Preformulation studies

Formulations	Angle of Repose(°)	Bulk density (g/ml)	Tapped density(g/ml)	Hausners ratio	Carr's Index (%)
F1	25.8	0.665	0.778	1.16	15.20
F2	23.6	0.65	0.750	1.15	15.78
F3	24.5	0.675	0.782	1.15	16.30

Table 4:Calibration Curve of Verapamil Hydrochloride

Concentration (µg/ml)	Absorbance (nm)
0	0
2	0.032
4	0.0706
6	0.0827
8	0.107
10	0.2128
20	0.3011
40	0.502
60	0.740
80	0.960

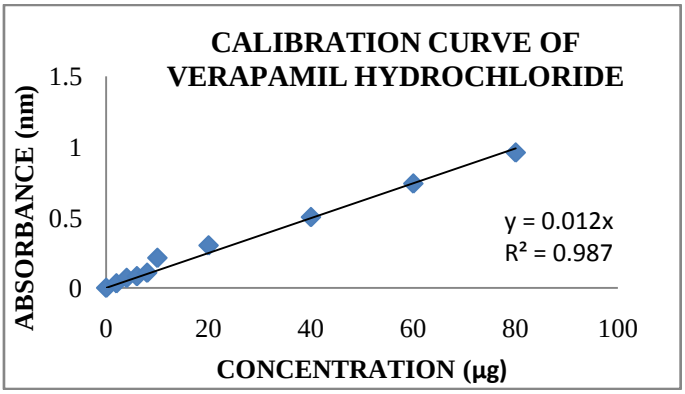

Fig 1:Calibration curve of verapamil hydrochloride in 0.1N HCl

Table 4:Physical properties of tablets

Property	FTV1	FTV2	FTV3
weightvariation	**±7.2**	**±6.5**	**±6.8**
Drug content(%)	98	102	101
Hardness(kg/cm^2)	6.1	5.9	6.3

Table5:Invitro Floating Ability Of Non Effervescent Floating Tablets Of Verapamil Hydrochloride

Formulation	Floating lag time	Total floating time
FTV1	127secs6	>12hrs
FTV2	160secs	>12hrs
FTV3	90secs	>12hrs

Table6 :In-vitro Dissolution Profile of Formulations (F1-F3)

TIME(hrs)	%CDR		
	FTV1	FTV2	FTV3
0	0	0	0
0.5	23.85	21.97	31.76
1	27.55	25.54	36.83
2	34.74	33.6	40.32
3	38.44	36.62	46.12
4	44	41.48	49.2
5	47.09	44.68	54.79
6	54.91	50.09	61.13
7	61.93	54.47	66.37
8	66.35	61.19	75.93

Kinetic Models For Formulations (FTV1-FTV3)-

Figure 3:Zero order plot for FTV1to FTV3

Figure 4:First order plot for F1tF3

Figure 5:Higuchi plot for F1to F3

Figure 6: Korse meyer peppas plot for F1to F3

Table 5:Results Of Kinetic Models Data For Formulations (F1-F3)-

Formulations	Zero order kinetics (R^2 value)	First order kinetics (R^2 value)	Higuchi (R^2 value)	Peppas model (R^2 value) (n value)	
F1	0.867	0.939	0.967	0.958	0.416
F2	0.806	0.907	0.914	0.912	0.400
F3	0.896	0.927	0.966	0.979	0.343

VIII. SUMMARY &CONCLUSION:

Various formulations of non effervescent floating tablets of Verapamil hydrochloride using peanut husk powder were formulated. The structural integrity of F1 was not maintained therefore the concentration of HPMC K_{100} M was increased in F2 & F3 to maintain structural integrity. The concentration of peanut husk powder was also increased in F2 & F3 to enhance total floating time and to reduce floating lag time as peanut husk powder aids in enhancing the floating property. Both F2 and F3 show excellent flow properties whereas F1 shows good flow properties. Based on the invitro dissolution profile obtained by performing dissolution studies F1, F2, F3 show %cumulative drug release(%CDR) of 66.35, 61.19 , 75.93 at 8hrs respectively. Based on R^2 values from Higuchi graphs drug release follows diffusion mechanism. Based on n values (n<=0.43) from Korse Meyer Peppas curves the diffusion is Fickian diffusion.

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