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PREPARATION CHARACTERIZATION AND EVALUATION OF CROSS LINKED STARCH UREA - A MODIFIED STARCH AS RATE CONTROLLING POLYMER FOR SUSTAINED RELEASE FLOATING TABLETS

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Abstract:

The objective of the present study is to prepare, characterize and to evaluate a new modified starch namely cross linked starch urea for its application in the formulation of sustained release floating tablets as rate controlling polymer. Cross linked starch urea was prepared and characterized by various physical properties and IR spectra. Sustained release floating tablets of three anti-hypertensive drugs namely Captopril, Losartan and Valsartan were formulated employing cross Linked starch Urea as rate controlling polymer and were evaluated.

Cross linked starch urea prepared by gelatinizing potato starch in the presence of urea and calcium chloride was insoluble in water and aqueous fluids of acidic and alkaline pHs. Cross linked starch urea exhibited good swelling in water. The swelling index was 630.2%. As crosslinked starch urea is insoluble and has good swelling in water, it is considered suitable as release retarding and rate controlling matrix polymer for sustained release floating tablets. stained release tablets of (i)captopril, (ii) losartan and (iii) valsartan prepared using cross linked starch urea as matrix polymer were non disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids and gave slow and controlled release over longer periods of time. In each case the release rate depended on the strength or concentration of cross linked starch urea polymer in the tablets. A good linear relationship was observed between percent polymer in the matrix tablets and release rate (K_0) with all the three drugs indicating that the cross linked starch urea polymer is an efficient rate controlling polymer suitable for design of sustained release tablets. Drug release from these SR tablets was by diffusion mechanism, fickian diffusion in the case of tablets containing low percent of polymer and non fickian (anamalous) diffusion in the case of tablets containing high percent of polymer.

Cross linked starch urea alone and in combination with sodium bicarbonate (gas generating agent) was found not suitable for formulation of floating tablets though it has good rate controlling effect for formulation of sustained release tablets. When cross linked starch urea was used along with bees wax (lipohilic polymer) and starch acetate (good film forming polymer) it was found suitable for formulation of floating tablets. Floating tablets formulated with cross linked starch urea (50%) as matrix polymer, Bees wax (5%) and starch acetate (5%) as floating enhancers and sodium bicarbonate as gas generating agent exhibited good floating over 13 – 14 hrs with a floating lag time of 45 – 60 seconds. Drug release from these floating tablets was spread over 12 hrs with all the three drugs studied. The drug release from these tablets was by non fickian (anomalous) diffusion. Thus cross linked starch urea was found to be a good rate controlling polymer for sustained release tablets and along with bees wax and starch acetate it was also a good matrix polymer for floating tablets.

Key words: *Cross linked starch urea, Sustained release floating tablets, Rate controlling polymer, Captopril, Losartan, Valsartan.*

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INTRODUCTION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms [1]. However the oral route of administration suffers with certain limitations such as short residence time of the dosage form in the g.i. tract, unpredictable gastric emptying, degradation of the drug due to highly reactive nature of g.i. contents and existence of an absorption window in the gastric and upper small intestine for several drugs. Gastric emptying is a complex process and makes *in vivo* performance of the drug delivery system uncertain. Formulation of floating drug delivery systems is a useful approach to avoid this variability with increased gastric retention time of the drug delivery system. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach 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 gastric residence time and a better control of the fluctuation in plasma drug concentration [2], [3]. Several approaches are currently used to retain the dosage in the stomach. These include bioadhesive systems, swelling and expanding systems , floating systems and other delayed gastric emptying devices[4],[5] .

The principle of floating tablets offers a simple and practical approach to achieve increased residence time in the stomach and upper g.i. tract to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer, a gas generating agent and a floating enhancer such as beeswax. Several polymers such as various viscosity grades of HPMC, Carbopol 934P, Eudragit RL, calcium alginate, Chitosan, Xanthan gum, guargum, etc., have been used in the design of floating tablets of various API. Sodium bicarbonate is the preferred gas generating agent in the formulation of floating tablets. Though a wide range of polymers are available there is a continued need to develop new and more efficient release retarding rate controlling polymers for sustained release floating tablets. The objective of the present study is to prepare, characterize and to evaluate a new modified starch namely cross linked starch urea for its application in the formulation of sustained release floating tablets as rate controlling polymer.

In the present study cross linked starch urea was prepared and characterized by various physical properties and IR spectra. Sustained release floating tablets of three anti-hypertensive drugs namely Captopril, Losartan and Valsartan were formulated employing cross Linked starch Urea as rate controlling polymer and were evaluated.

Captopril is an ACE inhibitor and is widely prescribed for the treatment of hypertension and congestive heart failure. Its duration of antihypertensive action after a single oral dose of Captopril is only 6 – 8 h. Clinical use requires a daily dose of 30 – 60 mg to be taken 2 - 3 times a day. It is most stable at pH 1.2 and as the pH increases, it becomes unstable and undergoes a degradation reaction[6]. Hence Sustained release Floating dosage form of captopril is needed to improve its bioavailability as well as to prolonged its duration of action.[7]. Losartan potassium is an orally active non- peptide angiotensin II receptor antagonist used in treatment of hypertension due to mainly blockade of AT1 receptors [8],[9]. The main limitation of low therapeutic effectiveness is due to narrow therapeutic index, poor bioavailability (25-35%), and short biological half life (1.5-2h). It is majorly absorbed from stomach and upper small intestine. Conventional tablets should be administered 3-4 times to maintain plasma drug concentration. To increase its oral bioavailability, therapeutic efficacy, reduce frequency of administration and for better patient compliance twice daily sustained release floating tablets of losartan potassium are needed. Valsartan is an angiotensin receptor blocker widely prescribed for hypertension. It is absorbed from stomach and upper small intestine[10],[11] . The oral bioavailability of valsartan was 23 %. It has a short biological half life of 3-6hrs[12],[13],[14]. Hence sustained release floating tablet formulation is needed for valsartan to enhance its oral bioavailability and to prolong its therapeutic effect, to reduce dosage frequency and to increase patient compliance.

MATERIALS AND METHODS:

Materials

Captopril, Losartan Potassium and Valsartan were gift samples from M/s Micro Labs Ltd, Pondicherry. Potato starch (Loba Chemie), Urea (Qualigens), Calcium Chloride I.P., Starch acetate (50 cps), Sodium bicarbonate, Lactose, Beeswax, Talc and Magnesium Sterate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

Preparation of Cross linked Starch urea polymer[15]

Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part), calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85^0C for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Characterization of cross-linked starch urea

The cross-linked starch urea prepared was characterized by microscopical examination, chemical and physical tests to determine its melting point, solubility, swelling index, pH, viscosity and various micromeritic properties namely bulk density, tap density, compressibility index and angle of repose and also by FTIR spectra.

1. Microscopic examination:

Slurry (1%) of each of (i) potato starch and (ii) cross-linked starch urea in a mixture of equal volumes of glycerin and water were prepared. A smear of the slurry was made and examined under microscope.

2. Chemical test:

Iodine test:

A slurry of cross-linked starch urea in water was treated with iodine test solution. A reddish violet colour was observed indicating the presence of α-amylose.

3. Melting point:

Melting point of crosslinked starch urea was determined in a melting point apparatus.

4. Solubility:

Solubility was tested in water, aqueous buffers of pH 1.2 and 7.4, methanol, petroleum ether, dichloromethane, cyclohexane and chloroform.

5. Swelling index:

Crosslinked starch urea(1g) was taken into two graduated 25ml measuring cylinders, one containing petroleum ether and other containing water and stored for 24 h. Swelling index of crosslinked starch urea was determined using the formula

$$\text{Swelling index (\%)} = \left(\frac{V_w - V_o}{V_o} \right) \times 100$$

Where, Vo is the volume of the sediment in petroleum ether and V_w is the volume of the sediment in water

6. pH:

The pH of a 0.1% w/v aqueous dispersion was measured.

7. Viscosity:

Viscosity of a 0.1%w/v homogenized dispersion was determined using Ostwald Viscometer.

8. Density (g/cc):

Density was determined by liquid displacement method using petroleum ether as liquid.

9. Bulk density:

Bulk and tap density was determined by 3 tap method in a graduated cylinder.

10. Compressibility index:

Compressibility index was determined by measuring the initial volume (Vo) and final volume (V) after 100 tappings of a sample of crosslinked starch urea in a measuring cylinder.

Compressibility index was calculated using the equation,

$$\text{Compressibilty index} = \frac{Vo - V}{Vo} \times 100$$

11. Angle of repose:

Angle of repose was determined by fixed funnel method. The physical and micromeritic properties of crosslinked starch urea prepared are summarized in Table 1.

12. Infrared Spectroscopy:

FTIR spectra of crosslinked starch urea was recorded on a Perkin Elmer, IR Spectrophotometer Model: Spectrum RXI, using KBr disc as reference.

Preparation of SR Tablets Using Cross Linked Starch Urea

Sustained release matrix tablets of (i) Captopril, (ii) Losartan and (iii) Valsartan were prepared by wet granulation method using cross linked starch urea as rate controlling matrix polymer as per the formulae given in Table 1.

In each case the drug, lactose and cross linked starch urea were thoroughly blended in a dry mortar. The blend was granulated with water (qs) to form wet granules. The wet granules were then dried at 70^0 for 1 hour. The dried granules were passed through mesh no 12 to break the aggregates and to form discrete granules. Talc and magnesium stearate were added to the dried granules and mixed. The tablet granulations were compressed into 400 mg tablets on a 8-station tablet punching machine (Karnavathi Rimek Minipress II) to a hardness of 4-5 Kg/cm^2. A total of 15 SR matrix tablets were prepared using cross linked starch urea as rate controlling matrix polymer.

Table 1: Formulae of Sustained Release Matrix Tablets of Selected Drugs formulated with cross Linked Starch - Urea

Ingredient (mg/tab)	**F1**	**F2**	**F3**	**F4**	**F5**
Drug (Captopril/ Losartan/ Valsartan)	80	80	80	80	80
Cross Linked Starch – Urea	100	132	200	264	300
Lactose	204	172	104	40	4
Talc	8	8	8	8	8
Magnesium stearate	8	8	8	8	8
Total weight (mg)	400	400	400	400	400

Preparation of Sustained Release Floating Tablets Using Cross Linked Starch Urea

Sustained release floating tablets of (i) Captopril, (ii) Losartan and (iii) Valsartan were prepared using cross linked starch urea as rate controlling matrix polymer, sodium bicarbonate as gas generating agent and bees wax and starch acetate as floating enhancers as per the formulae given in Table 2. In each case formulations FF1 and FF2 were prepared by wet granulation method as described above under preparation of SR tablets. Formulations FF3 and FF4 in each case were prepared by melt – wet granulation method as follows.

Table 2: Formulae of Sustained Release Floating Tablets of Selected Drugs Prepared with cross Linked Starch - Urea

Ingredient (mg/tab)	**FF1**	**FF2**	**FF3**	**FF4**
Drug (Captopril/ Losartan/ Valsartan)	80	80	80	80
Cross Linked Starch – Urea	200	200	200	200
Sodium Bicarbonate (15%)	-	60	60	60
Bees Wax (5%)	-	-	20	20
Starch Acetate (5%)	-	-	-	20
Lactose	104	44	24	4
Talc	8	8	8	8
Magnesium stearate	8	8	8	8
Total weight (mg)	400	400	400	400

The required quantities of drug, Cross linked starch-urea, starch acetate, lactose and sodium bicarbonate were thoroughly mixed in a dry mortar by following geometric dilution technique. Beeswax was melted in a dry beaker and the blend of the above mentioned ingredients was added to the molten beeswax and mixed thoroughly. The blend was transferred to a dry mortar and granulated with hydro-alcoholic (1:1) solution. The dried granules formed were passed through mesh No. 16 to break the aggregates. The lubricants talc and magnesium stearate were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were then compressed into 400mg tablets on a 8-station tablet punching machine (Karnavathi Rimek Minipress II) to a hardness of 4-5 Kg/cm^2.

Evaluation of Tablets

Hardness of the tablets was tested using a Monsanto hardness tester.

Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a Paramount tablet disintegration test machine using water, 0.1N HCl (pH 1.2) and phosphate buffer of pH 7.4 as the test fluids.

Estimation of Durg Content

UV Spectrophotometric methods were used for the estimation of (i) Captopril at 215 nm, (ii) Losartan at 234 nm and (iii) Valsartan at 250 nm. The methods obeyed Beer-Lambert's law in the concentration range of 0-10 µg / mL in each case. When a standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be in the range 0.60% - 0.85 % and 1.2% - 1.60% respectively. No interference from the excepients used was observed.

Floating Lag Time and Floating Time

In Vitro buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 ml glass beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration in which the tablet remains floating was determined as floating time.

Drug Release Study

Drug release from all the sustained release floating tablets prepared was studied using 8-station dissolution rate test apparatus (Labindia, DS 8000) employing a paddle stirrer at 50 rpm and at a temperature of 37±1^{0}C. Hydrochloric acid, 0.1 N (900 mL) was used as dissolution fluid. A 5mL aliquot of dissolution medium was withdrawn through a filter (0.45µm) at different time intervals and assayed spectrophotometrically by measuring absorbance at 215 nm in the case of Captopril, at 234 nm in the case of Losartan and 250 nm in the case of Valsartan. All drug release experiments were conducted in triplicate (n=3).

Data Analysis

Drug release data were analysed as per Zero order, first order. Higuichi[16] and Korsemeyer - Peppas[17] equation models to assess drug release kinetics and mechanism from the floating tablets prepared.

RESULTS AND DISCUSSION:

Starch urea cross-linked with calcium was prepared by gelatinizing potato starch in the presence of urea and calcium chloride. It is known[18],[19] that starch reacts with urea to form starch carbamate, a starch urea polymer. Khalil et al.[20] investigated the reactions between starch and urea resulting in the formation of starch urea (starch carbamate). The reactions involved are as follows

$$St\ OH + CO\ (NH_2)_2 \overset{heat}{\leftrightarrow} St\ OCONH_2 + NH_3$$

$$2\ St\ OCONH_2 \overset{heat}{\rightarrow} St\ OCONHCOO\ St + NH_3$$

$$St\ OH + St\ OCONH_2 \overset{heat}{\rightarrow} St\ OCOO\ St + NH_3$$

Where St OH is starch

Starch urea was cross linked by treatment with calcium chloride. The formation of cross-linked starches with calcium salts is known in polymer chemistry. As the cross-linked polymers generally swell in water and aqueous fluids and form gelatinous matrices suitable for controlled release, it is thought worthwhile to investigate starch urea cross-linked with calcium chloride for its application in Sustained release floating tablets. In the present study it was evaluated as rate controlling matrix polymer in the preparation of sustained release tablets and sustained release floating tablets.

The crosslinked starch urea prepared was found to be fine, hard and free flowing crystalline powder. The physical and micromeritic properties of crosslinked starch urea prepared are summarized in Table 1.

It gave a positive iodine test indicating the presence of α-amylose. The FTIR spectra of cross linked starch urea is shown in Fig.1. The presence of IR absorption peaks at 3369.05 cm^{-1} due to –NH_2 and at 1668.72 cm^{-1} due to –C=O stretch indicated the presence of urea in the polymer. The peaks at 2925.84 cm^{-1} (C-H stretch) and 1271.99 cm^{-1} (C-O-C) indicate the presence of α-amylose. When tested for melting point, cross linked starch urea charred at 210^{0}C.

Microscopic examination indicated that potato starch consists of oval shaped grains . Whereas crosslinked

starch urea consists of rectangular, transparent crystals .

It was insoluble in water, aqueous fluids of acidic and alkaline pHs. It was insoluble in organic solvents like methanol, petroleum ether, dichloromethane, cyclohexane and chloroform. The pH of a 0.1% aqueous dispersion was 9.10. Crosslinked starch urea exhibited good swelling in water. The swelling index was 630.2%. All micromeritic properties indicated good flow and compressibility needed for solid dosage form manufacturing.

Table 3: Physical and Micromeritic Properties of Cross-linked Starch urea

S.No	Property	Result
1.	Iodine test	Positive indicates the presence of α-amylose
2.	Melting point	Charred at 210^0C
3.	Solubility	Insoluble in water, aqueous fluids of acidic and alkaline pHs and in organic solvents
4.	Swelling index	Swells in water with a swelling index of 630.2 %
5.	pH of 0.1 % aqueous dispersion	9.10
6.	Viscosity of a 0.1 % aqueous dispersion	1.013cps
7.	Density	0.516 g/cc
8.	Bulk density	0.735 g/cc
9.	Compressibility index	13.89 %
10.	Angle of repose	26^0 - 27^0

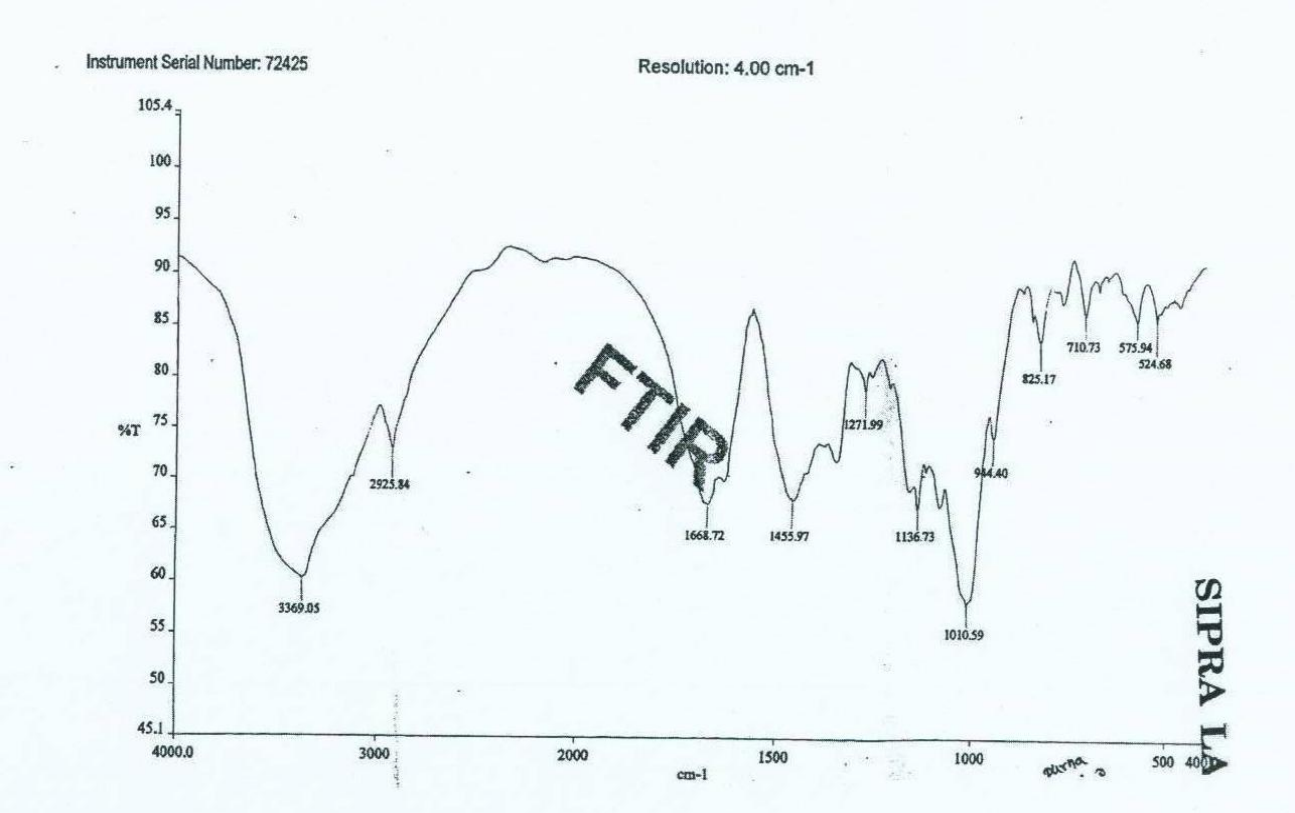

Fig 1: FTIR spectra of cross linked starch Urea

As crosslinked starch urea is insoluble and has good swelling in water, it is considered suitable as release retarding and rate controlling matrix polymer for sustained release and floating tablets.

Evaluation of Cross Linked Starch Urea as Rate controlling Polymer in SR Tablets:

Sustained release matrix tablets of (i) Captopril, (ii) Losartan and (iii) Valsartan were prepared by wet granulation method using cross linked starch urea as rate controlling matrix polymer as per the formulae given in Table 2. In each case cross linked starch urea polymer was used in different strengths (25, 33, 50, 66 and 75 % w/w). A total of 15 SR tablet formulations were prepared using cross linked starch urea. The physical parameters of the sustained release tablets prepared with cross linked starch urea are given in Table 4. The hardness of the tablets was in the range 4.0 – 5.5 kg/ cm^2. Percent weight loss in the friability test was in the range 0.25 – 0.70 %. Drug content of the tablets prepared was with in 100 ± 2 % of the labelled content. The tablets prepared were non disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such the tablets prepared with cross linked starch urea are found suitable for sustained release application.

In vitro drug release rate of the prepared tablets were studied in 0.1 N HCl (representing stomach pH). The drug release profiles of various tablets prepared are shown in Figs. 2-4. With all the three drugs studied (Captopril, Losartan and Valsartan) the release from the SR tablets formulated with Cross linked starch urea was slow and spread over longer periods of time. The release rate depended on the strength or concentration of cross linked starch urea polymer in the tablets. The release data in each case were analysed as per zero order, first order, Higuchi and Korsemeyer- Peppas equation models. The drug release parameters of various tablets are shown in Table 4.

Table 4: Physical and Release Parameters of Sustained Release matrix tablets of selected drugs formulated using cross linked starch urea

Formulation	Hardness (Kg/cm^2)	Friability (% wt. loss)	Drug Content (mg/tablet)	T_{50} (h)	Release Rate		Release Exponent (n)
					Ko (mg/h)	K1(h^{-1})	
CF1	4.5	0.55	80.20	0.75	19.10	0.94255	0.54
CF2	5.0	0.65	80.80	1.8	8.40	0.48644	0.31
CF3	5.5	0.58	79.60	3.8	6.12	0.29076	0.49
CF4	5.0	0.48	80.45	5.0	5.12	0.15764	0.51
CF5	5.0	0.50	79.55	7.0	4.81	0.11753	0.60
LF1	5.0	0.45	80.65	0.75	23.41	0.70503	0.35
LF2	4.5	0.40	81.05	1.5	10.82	0.35079	0.38
LF3	4.0	0.65	81.50	4.0	7.66	0.1693	0.57
LF4	5.5	0.45	79.45	5.5	6.18	0.12147	0.57
LF5	5.0	0.25	79.65	7.0	5.65	0.08876	0.71
VF1	5.0	0.70	80.50	0.75	23.98	0.92499	0.26
VF2	5.5	0.58	79.45	1.5	10.50	0.48644	0.30
VF3	4.5	0.40	78.65	3.0	7.18	0.29076	0.48
VF4	5.5	0.65	80.25	4.0	6.28	0.15764	0.51
VF5	4.0	0.70	80.95	5.5	5.68	0.12664	0.60

CF1–CF5: Captopril SR tablets; LF1-LF5: Losartan SR Tablets;VF1-VF5: Valsartan SR Tablets.

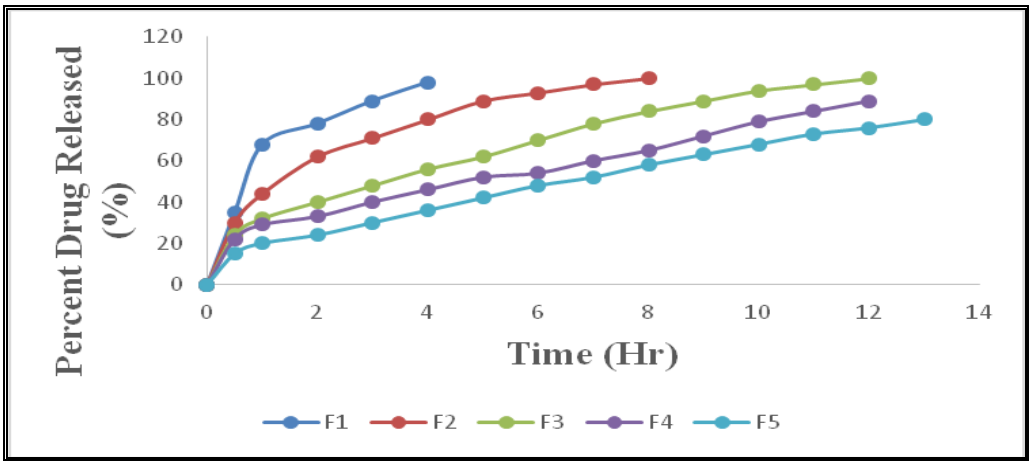

Fig 2: Drug Release Profiles of Sustained Release Captopril Tablets Formulated Using Cross Linked Starch Urea

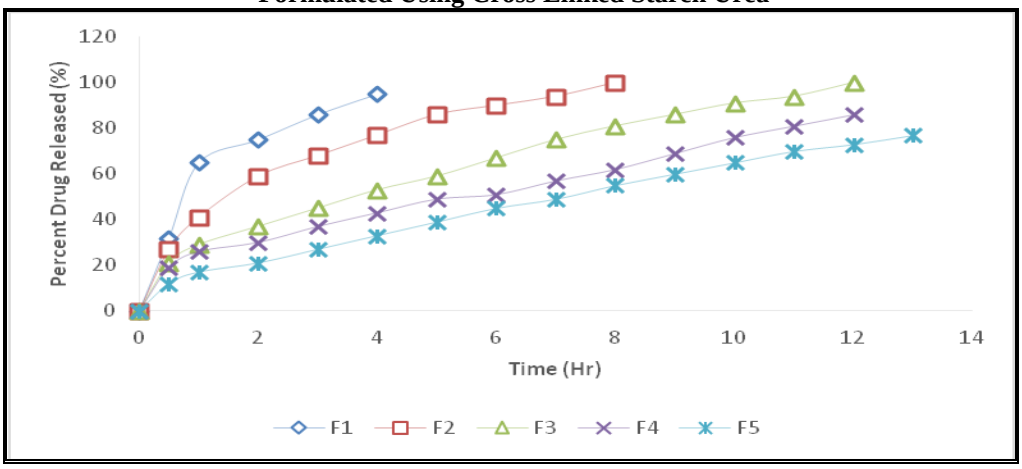

Fig 3: Drug Release Profiles of Sustained Release Losartan Tablets Formulated Using Cross Linked Starch Urea

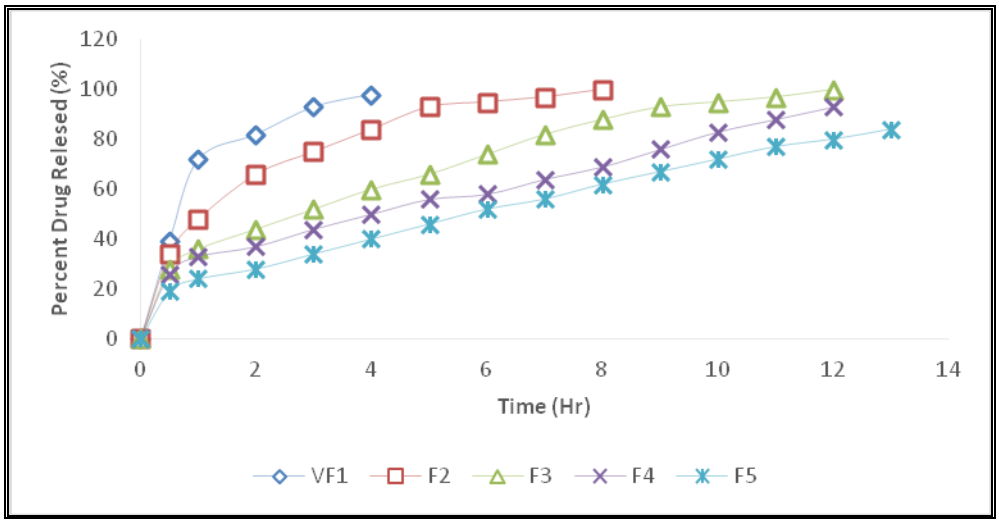

Fig 4: Drug Release Profiles of Sustained Release Valsartan Tablets Formulated Using Cross Linked Starch Urea

A good linear relationship between percent polymer in the tablets and drug release rate (K_0) with all the three drugs as shown in fig: 5

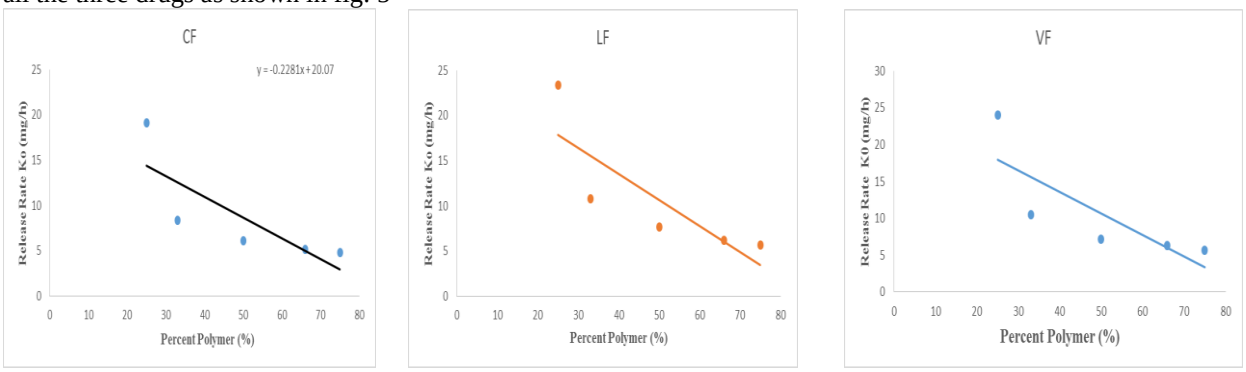

Fig 5: Relationship between percent polymer in the tablets and release rate K_0; CF : Captopril tablets, LF : Losartan Tablets, VF : Valsartan Tablets.

Good linear relationship between percent polymer in the matrix tablets and release rate (K_0) indicate that the cross linked starch urea polymer is an efficient rate controlling polymer suitable for design of sustained release tablets. Linear Higuchi plots with R^2 = > 0.9725 indicated diffusion controlled drug release from all the sustained release tablets formulated using cross linked starch urea. Release exponent (n) in the analysis of release data as per korsemeyer-Peppas equation indicated fickian diffusion as the release mechanism in formulations F1 and F2, which exhibited relatively fast drug release. Non fickian (anomalous) diffusion was a release mechanism from the tablets F3 and F4 in each case which gave relatively slow release.

Evaluation of Cross Linked Starch Urea As Matrix Polymer For Floating Tablets:

Sustained release floating tablets of (i) Captopril, (ii) Losartan and (iii) Valsartan were prepared using cross linked starch urea as rate controlling matrix polymer, sodium bicarbonate as gas generating agent and bees wax and starch acetate as floating enhancers as per the formulae given in Table 3. The floating tablets prepared were evaluated for various physical parameters including floating lag time and floating time and also for drug release characteristics. The physical and release parameters of the floating tablets prepared are given in Table 5.

Table 5: Physical and Release Parameters of Sustained Release Floating tablets of selected drugs formulated using cross linked starch urea

Formu-lation	Hard -ness (Kg/cm)	Fria bility (%wt.loss)	Drug Content (mg/tablet)	Floating lag time (sec)	Floating Time (h)	T_{50} (h)	Release Rate		Release Exponent (n)
							Ko (mg/h)	K1 (h^{-1})	
CFF1	5.0	0.65	80.50	No Floating	No Floating	3.2	5.89	0.2728	0.54
CFF2	5.5	0.25	80.20	Disintegr-ated	Disintegr-ated	0.75	17.52	0.8459	0.21
CFF3	4.5	0.35	79.20	120	8.0	1.50	8.86	0.5021	0.41
CFF4	5.0	0.40	80.40	45	14.0	5.0	5.33	0.1729	0.62
LFF1	5.5	0.45	80.60	No Floating	No Floating	3.5	5.90	0.0998	0.57
LFF2	4.0	0.50	81.00	Disintegr-ated	Disintegr-ated	0.75	17.43	0.8960	0.29
LFF3	4.5	0.65	81.50	135	10.0	1.50	8.97	0.5574	0.39
LFF4	5.0	0.35	79.40	50	13.0	5.0	5.94	0.2447	0.70
VFF1	4.5	0.45	80.50	No Floating	No Floating	2.5	5.75	0.2907	0.45
VFF2	5.0	0.70	79.20	Disintegr-ated	Disintegr-ated	0.6	17.20	1.0562	0.17
VFF3	4.5	0.60	78.60	140	8.0	2.0	7.67	0.4521	0.46
VFF4	4.5	0.63	80.70	60	13.0	5.0	5.67	0.1704	0.50

CFF1–CFF5: Captopril SR Floating tablets; LFF1-LFF5: Losartan SR Floating Tablets; VFF1-VFF5: Valsartan SR Floating Tablets.

With all the three drugs, no floating was observed with the floating tablets formulated using cross linked starch urea alone (CFF1, LFF1 and VFF1). Formulations CFF2, LFF2 and VFF2 contain sodium bicarbonate (15 %) as gas generating agent in addition to cross linked starch urea (50 %) as matrix polymer. These tablets disintegrated during buoyancy test and gave rapid drug release in drug release study. Formulations CFF3, LFF3 and VFF3 also contain Bees wax (5%) as floating enhancer. These tablets exhibited a good floating over 8-10 hrs with a floating lag time of 120 – 140 seconds. Formulations CFF4, LFF4 and VFF4 contain starch acetate (5%) as floating enhancer and also to retard drug release from the tablets. These tablets exhibited floating over 13-14 hrs with a floating lag time of 45-60 seconds i.e., less than 1 min.

Thus, cross linked starch urea alone and in combination with sodium bicarbonate (gas generating agent) was found not suitable for formulation of floating tablets though it has good rate controlling effect for formulation of sustained release tablets. When cross linked starch urea was used along with bees wax (lipohilic polymer) and starch acetate (good film forming polymer) it was found suitable for formulation of floating tablets. Floating tablets formulated with cross linked starch urea (50%) as matrix polymer, Bees wax(5%) and starch acetate (5%) as floating enhancers and sodium bicarbonate as gas generating agent exhibited good floating characteristics.

Drug release from all the floating tablets prepared was studied in 0.1 N HCl. Drug release profiles of various floating tablets prepared are shown in Figs 5-7. The release parameters are given in Table 5. Formulations CFF2, LFF2 and VFF2 which contain sodium bicarbonate and cross linked starch urea alone gave rapid release and release from these tablets was by fickian diffusion.

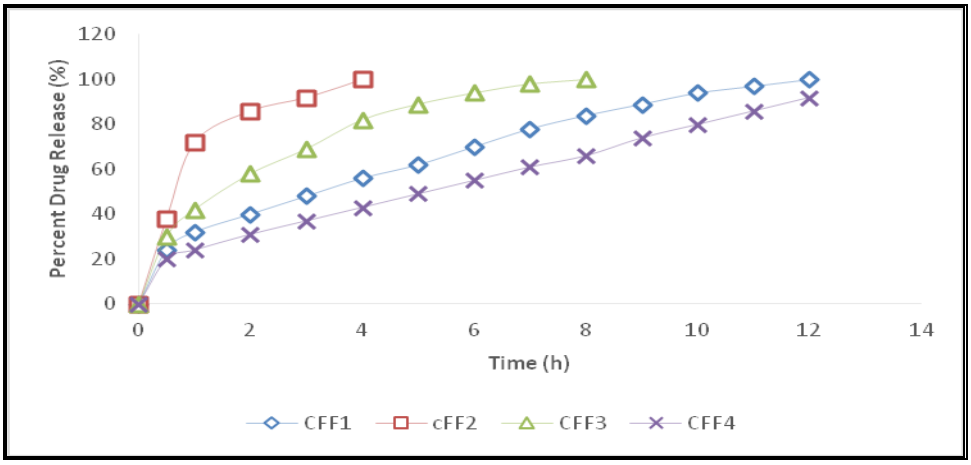

Fig :6 Drug Release Profiles of Sustained release Floating Tablets of Captopril formulated using Cross Linked Starch Urea

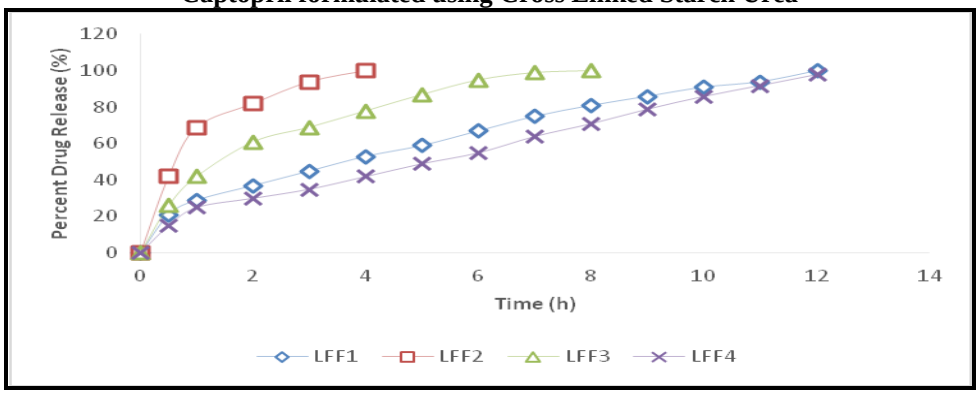

Fig :7 Drug Release Profiles of Sustained release Floating Tablets of Losartan formulated using Cross Linked Starch Urea

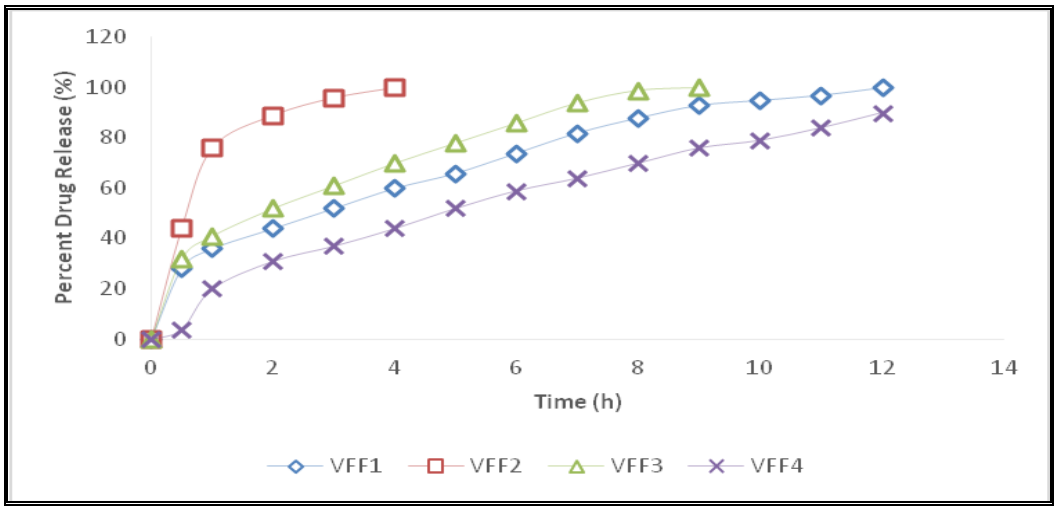

Fig :8 Drug Release Profiles of Sustained release Floating Tablets of Valsartan formulated using Cross Linked Starch Urea

Drug release from formulations CFF4, LFF4, and VFF4 which contain bees wax and starch acetate in addition to cross linked starch urea gave slow release over 12hrs and the drug release from these tablets was by non fickian (anomalous) diffusion.

CONCLUSIONS:

1. Cross linked starch urea prepared by gelatinizing potato starch in the presence of urea and calcium chloride was insoluble in water and aqueous fluids of acidic and alkaline pHs. Cross linked starch urea exhibited good swelling in water. The swelling index was 630.2%. As crosslinked starch urea is insoluble and has good swelling in water, it is considered suitable as release retarding and rate controlling matrix polymer for sustained release floating tablets.
2. sustained release tablets of (i)captopril, (ii) losartan and (iii) valsartan prepared using cross linked starch urea as matrix polymer were non disintegrating in water, acidic (pH 1.2) and alkaline (pH 7.4) fluids and gave slow and controlled release over longer periods of time. In each case the release rate depended on the strength or concentration of cross linked starch urea polymer in the tablets.
3. A good linear relationship was observed between percent polymer in the matrix tablets and release rate (K_0) with all the three drugs indicating that the cross linked starch urea polymer is an efficient rate controlling polymer suitable for design of sustained release tablets.
4. Drug release from these SR tablets was by diffusion mechanism, fickian diffusion in the case of tablets containing low percent of polymer and non fickian (anamalous) diffusion in the case of tablets containing high percent of polymer.
5. Cross linked starch urea alone and in combination with sodium bicarbonate (gas generating agent) was found not suitable for formulation of floating tablets though it has good rate controlling effect for formulation of sustained release tablets.
6. When cross linked starch urea was used along with bees wax (lipohilic polymer) and starch acetate (good film forming polymer) it was found suitable for formulation of floating tablets.
7. Floating tablets formulated with cross linked starch urea (50%) as matrix polymer, Bees wax (5%) and starch acetate (5%) as floating enhancers and sodium bicarbonate as gas generating agent exhibited good floating over 13 – 14 hrs with a floating lag time of 45 – 60 seconds. Drug release from these floating tablets was spread over 12 hrs with all the three drugs studied. The drug release from these tablets was by non fickian (anomalous) diffusion.
8. Thus cross linked starch urea was found to be a good rate controlling polymer for sustained release tablets and along with bees wax and starch acetate it was also a good matrix polymer for floating tablets.

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