# SELF SWELLING DUAL RESPONSIVE POLY-(ACRYLIC ACID-CO-ACRYLAMIDE): A NOVEL HYDROGEL IN DRUG DELIVERY SYSTEM

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**Abstract -** Polymers have been reported as ubiquitous materials on earth. Hydrogels include one of those types of polymers which can absorb and release ample amount of solvent. These hydrogels come from a superior class of Smart polymers which have gathered great value of interest in varieties of significant applications like drug delivery, tissue engineering etc. Poly-(acrylic acid-co-acrylamide) (PAA-co-AAm) a self swelling hydrogel was synthesised by free radical polymerisation. This hydrogel tends to absorb water above room temperature. It also exhibits a change in phase (hazy to clear) at higher temperature. Effect of change in amount of acrylamide was investigated to observe the fluctuation in absorption and desorption behaviour of hydrogel. The hydrogel with 4% acrylamide showed desorption from the onset of 40°C. This hydrogel was then tested for delivering Nexpro Fast 20 (antacid) in a simulated gastric fluid (SGF) pH=2.5. An increase in pH (2.5-3.65) of SGF was observed at a temperature of 40°C in 10 min. These observations suggested that PAA-co-AAm hydrogel can have a potential for transporting stomach specific drugs.

**Keywords** - Hydrogels, Poly-(Acrylic Acid-co-Acrylamide), Simulated Gastric Fluid, Drug Delivery.

## I. INTRODUCTION

Polymer science has become a part of immense research since its inception. Polymers are excellent class of high molecular weight organic materials providing high performance characteristics without much difficulty in production, handling and disposal [**1**]. Smart polymers or stimuli responsive polymers come into the category where polymers respond to a slight change in stimulus like temperature, pH, ionic strength, electric field etc. This response can be a change in structure, shape or phase [**2-4**]. These smart polymers include another fascinating type of polymers with a three dimensional cross linked structure with ability to retain sufficient amount of water. They are called hydrogels [**5**]. These hydrogels have consistently being employed in water absorbing diapers, water beads for plants, delivery of therapeutics, flocculants and dispersants for treating waste water and also in tissue engineering [**6**]. Based on their method of preparation hydrogels can be homopolymer, copolymer, semi-interpenetrating network and interpenetrating network [**7**]. Copolymer hydrogels have been synthesised and investigated by *W. Li et al* for environmental analysis [**8**] and *Yongsheng Wang et al* for removal of dye from aqueous solution [**9**]. Their unique properties of absorption as well as adsorption and response to change in pH render these smart materials for unique applications [**10, 11**]. These properties are acknowledged by the fact that these polymers tend to respond to changes in external stimulus like temperature and pH hence known as Thermo-responsive and pH responsive polymers. A slight fluctuation in temperature triggers these polymers to undergo a change in structure, shape, and phase. The temperature at which such changes are observed is termed Critical Solution Temperature. There exist two temperatures: Lower Critical Solution Temperature (LCST) and Upper Critical Solution Temperature (UCST). LCST is minimum temperature below which the polymer imbibe water and above which it expels it. Similarly UCST is maximum temperature above which the polymer absorbs water and below which it desorbs in water or aqueous solutions [**12**]. Polymers or more correctly hydrogels which exhibit temperature and pH responsiveness have been frequently relied upon to deliver therapeutics and classical drugs within fluctuating physiological environment of human body [**13**].

Poly-N, isopropylacrylamide (PNIPAM) is an excellent example of LCST polymer which has transition temperature of 37°C close to that of human body hence it has been exploited by *Bao-Lin Guo et al* for oral delivery of drug [**14**]. Hydrogel for delivering stomach specific anticancer drug have also been synthesised and studied by *P. Ravichandran et al* [**15**]. Similarly PAA-co-AAm is another example of polymer which has a UCST of 25°C [**12**].

Monomers which have carboxylate functional group (-COOH-) readily combine with themselves by reacting with double bonds to undergo cross linking and form dense network of polymer chains [**16**] where as polymers of acrylamide are synthesised as viscous gels [**17**]. Hence PAA-co-AAm is synthesised in a gel like form.

In this manuscript a self swelling PAA-co-AAm hydrogel was synthesised by in situ free radical solution polymerisation. The hydrogel was then tested for its phase transition to confirm its UCST

behaviour. The effect of variation in acrylamide content on tuning of transition temperature and absorption behaviour was studied. Simultaneously the effect of acrylamide content on percent conversion of hydrogel during synthesis was also studied and graph was plotted to compare the results. Finally from optimum results one of the hydrogel was chosen as a carrier to study in vitro release of Nexpro fast 20 (chosen as model antacid) in Simulated gastric fluid (SGF). The results suffice that this hydrogel can be utilised as an effective carrier for delivering stomach specific drugs.

## II. MATERIALS AND METHODS

### *2.1 Materials*

Acrylic acid (AA), acrylamide (AAm), potassium persulfate (KPS), sodium metabisulfite (SMS), sodium hydroxide (NaOH), methanol ($CH_3OH$), hydrochloric acid (HCL) (All these chemicals were purchased from Central Scientific, Ramdaspeth Nagpur), Nexpro fast 20 (an antacid purchased from Prachi Medical, Nagpur). All the solutions were prepared in deionized water.

### *2.2 Synthesis of PAA-co-AAM hydrogel*

0.16 mol AA and 0.002 mol AAm was taken in a beaker containing 15 ml deionized water. 0.5% KPS and 0.25% SMS was dissolved in a beaker filled with 90 ml deionized water. This solution was transferred to a 3-neck round bottom flask equipped with mechanical stirrer, water condenser, heating mantle with thermocouple probe. The solution was heated to 60°C under vigorous agitation. At 60°C monomers were added from the beaker and pH of the solution was adjusted by adding NaOH. Methanol was added in slight amount to dehydrate the system and relieve the product from over drying. The solution was purged with helium gas to make the apparatus oxygen-free which tends to inhibit the polymerisation reaction. Temperature was maintained at 70°C for 4 hr to carry out polymerisation. After 4 hr whitish viscous gel like solution was obtained which was poured off and washed with ethanol. The product was then oven dried at 85°C overnight. The hydrogel obtained was non-flowing, sticky and highly viscous. The product was again washed with water and then ethanol to remove moisture. Similar procedure was carried out by varying acrylamide content (1.5%, 2%, 4%, and 6% of acrylic acid). **Fig 1** shows molecular structure of PAA-co-AAm.

### *2.3 Conversion of hydrogel*

While carrying out the synthesis of hydrogel after every 30 min a slight amount of sample from reaction mixture was drawn out on watch glass and weighed before and after drying it in oven at 85°C. Percent conversion of sample was then calculated as suggested by *Naziha Chirani et al* **[6].**

$$\% \text{ conversion} = \frac{\text{Sample weight after drying} - (\text{weight \% of KPS + SMS})}{(\text{Initial sample weight x weight \% of solids}) - (\text{weight \% of KPS + SMS})} \quad (1)$$

The calculated values were noted down in **table 1**.

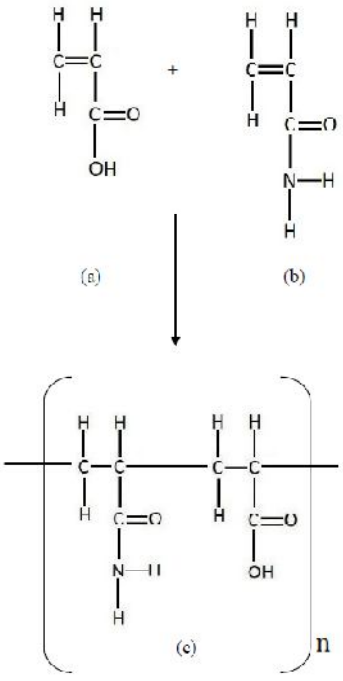



**Figure 1: Molecular structures of (a) Acrylic Acid, (b) Acrylamide, (c) PAA-co-AAm**

### *2.4 Swelling of PAA-co-AAm hydrogel*

An appropriate weight of hydrogel from each batch was transferred to a beaker containing 20 ml of deionised water. The beaker was covered from top and placed in water bath for appropriate control of temperature. The temperature of water bath was raised gradually and for every 10°C rise in temperature the hydrogel was weighed and noted. The swell content of hydrogel was calculated by a method suggested by *Jianjun Xie et al* [**10**].

$$\text{Swell content} = \frac{W_s - W_d}{W_d} \quad (2)$$

Where $W_s$ was weight of swollen hydrogel after certain time t seconds, $W_d$ was weight of dry hydrogel. **Table 2** shows swell content of hydrogel noted as gram of water absorbed per gram of hydrogel.

| | Conversion (%) | | | |
|---|---|---|---|---|
| Time (min) | 1.5% AAm | 2% AAm | 4% AAm | 6% AAm |
| 0 | 0 | 0 | 0 | 0 |
| 30 | 12.20 | 22.46 | 67.35 | 41.52 |
| 60 | 33.37 | 49.76 | 78.93 | 60.79 |
| 90 | 45.35 | 50.55 | 89.77 | 80.88 |
| 120 | 50.55 | 52.27 | 90.22 | 97.80 |
| 150 | 70.89 | 63.35 | 95.74 | 98.60 |
| 180 | 79.88 | 69.15 | - | - |
| 210 | 84.57 | 79.89 | - | - |
| 240 | 90.60 | 87.17 | - | - |
| 270 | 91.61 | 98.87 | - | - |
| 300 | 97.20 | - | - | - |

**Table 1: Percentage conversion with time of PAA-co-AAm with various AAm content.**

### *2.5 Phase transition of hydrogel*

**Fig 2** shows the phase transition of PAA-co-AAm hydrogel. Hydrogel was placed on a petri-dish (**fig 2a**) and heated in oven until a clear transparent phase was observed (**fig 2b**). It was then allowed to be cooled (**fig 2c**). Upon cooling a slight whitish portion inside the hydrogel appeared (**fig 2d**) which slowly started to propagate (**fig 2e**) and the entire whitishness of original product was recovered after complete cooling (**fig 2f**). This corresponded to change in phase upon change in temperature which is known as thermo responsiveness [**12**].

### *2.6 In-vitro drug release*

Nexpro fast 20 was chosen as a model drug (antacid) to carry out its release in a prepared SGF. The drug was peeled off to remove its outer coating and dissolved in 20 ml deionized water. PAA-co-AAm (4% acrylamide chosen from optimum results) was taken in a beaker (**fig 5a**) and 5 ml of solubilised drug was injected into it simultaneously by rising the temperature upto 35°C. Excess drug was removed from beaker. Drug loading was confirmed by inspection of transparent phase and swelling of hydrogel by fine bubbles of drug inside the hydrogel matrix (**fig 5b**). SGF (pH=2.5) was prepared by adding 0.1N HCL into deionized water. A human body has 35±7 ml of gastic fluid on empty stomach so 40 ml of SGF was best chosen to be tested within. 40 ml SGF was transferred to beaker having drug loaded hydrogel and temperature was kept upto 40°C i.e. close to human body (**fig 5c**).

## III. RESULTS AND DISCUSSION

### *3.1 Effect of temperature on phase of hydrogel*

By carrying out phase transition test it can be inferred that beyond UCST PAA-co-AAM hydrogel undergoes a change in physical appearance to become clear and transparent. This behaviour relates to absorption of water between a cluster of $–COO^-$ ionic bond of acrylic acid within polymer matrix and hydrogen bond within water. At the peak level clear transparent phase becomes obvious (**fig 2b)**. The reverse of it happens upon cooling. Lowering of temperature results in diminishing the interaction between polymer and water as a result of which hazy phase starts to appear (**fig 2c**). Further lowering of temperature goes to show propagation of hazy phase of hydrogel (**fig 2d**) and by the time complete cooling has been achieved, the interaction between water and polymer breaks as a result of which water is expelled out and original hazy appearance of the hydrogel is restored (**fig 2e** and **fig 2f**). From thermodynamic point of view at higher temperature there exist a balance between entropic effect due to absorption and ordered state of water molecules in the vicinity of polymer matrix while enthalpy effects are balanced by inter and intra molecular forces due to solvation, hydrogen bonding and hydrophobic interaction [**12**].

### *3.2 Effect of AAm content on conversion profile*

From **fig 3** it was observed that hydrogel with 1.5% AAm content took longer time to achieve more than 90% conversion and the order was followed in a decreasing fashion as 2%, 4%, 6% AAm. From kinetic study of polymerisation it can be stated that rate of reaction is proportional to concentration of monomer. Hence more the amount of monomer faster is the rate of reaction [**1**]. However conversion upto 85% of hydrogel with 4% AAm content was observed first than hydrogel with 6% AAM. This fact can be attributed to intramolecular transfer reaction also called as backbiting of chains while polymerization of acrylic monomers which resulted in slow down of rate of reaction and ultimately the rate of polymerisation [**18**].

(a)

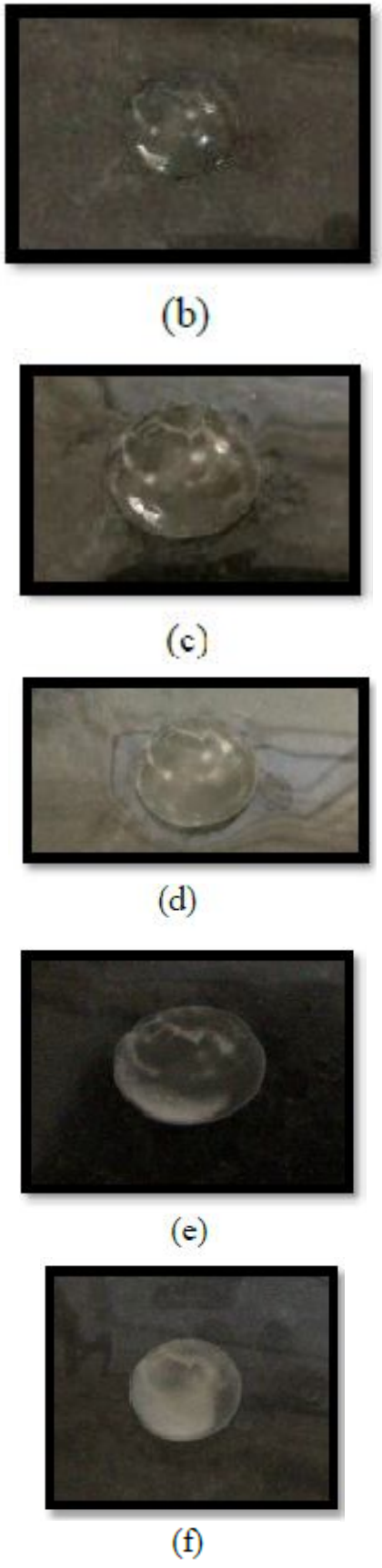



**Fig 2: Phase transition of hydrogel (hazy to clear). (a) Dry hydrogel at room temperature, (b) Heated above UCST, (c) Cooling with water, (d) Onset of hazy phase, (e) Propagation of hazy phase, (f) Complete recovery of hazy phase**

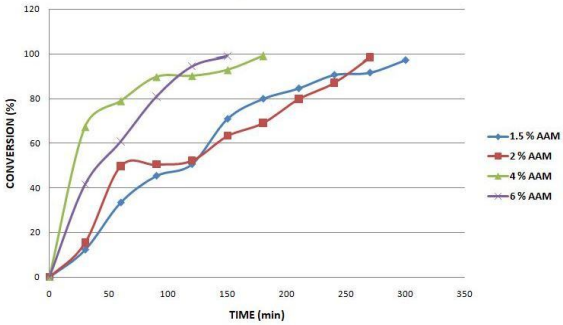



**Fig 3: Conversion versus time graph of PAA-co-AAm with varying AAm content**

### *3.3 Effect of AAm content on tuning of transition temperature*

From **fig 3** it was seen that hydrogel with 4% AAm showed faster conversion than corresponding 1.5% and 2% ones. Also as noticed from **fig 4** this 4% AAm hydrogel not only exhibited desorption above 39°C unlike other hydrogels, it also exhibited steady swell rate between 30°C and 40°C. It can be said that higher amount of AAm resulted in intense solidification of hydrogel which showed a reduced absorption/swelling even at high temperature (**fig 4**). Interestingly a steady swell rate indicated that swollen hydrogel cannot undergo absorption until 39°C temperature is reached. This means no other fluid can travel inside the hydrogel once the steady state is achieved. Also converse of the same is true that no fluid can come out of hydrogel at steady swell rate. Upon further rise in AAm content no such aberrant effect of deswelling was noted in the current investigation.

### *3.4 Swelling behaviour of PAA-co-AAm hydrogel*

**Table 2** shows result of swelling/absorption behaviour of hydrogels with varying AAm content. Hydrogel with 1.5% AAm has undergone 24.25% swelling from 20-40°C while further rise in temperature exhibited deswelling/desorption. The one with 2% AAm showed

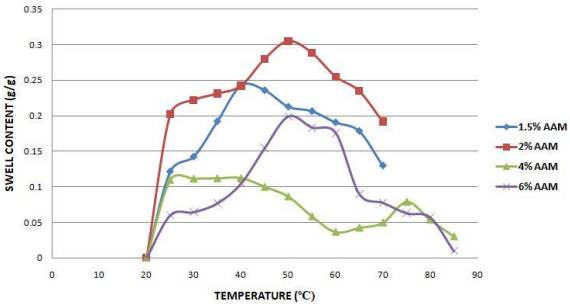



**Fig 4: Effect of AAm content on swelling behaviour of PAA-co-AAm hydrogel**

30.47% swelling from 20-50°C and beyond this temperature deswelling as usual have been reported. But hydrogel containing 4% AAm although showed appreciable absorption from 20-25°C but after passing the steady swelling rate in the range of 30-39 °C it skipped the swelling behaviour beyond 40°C.

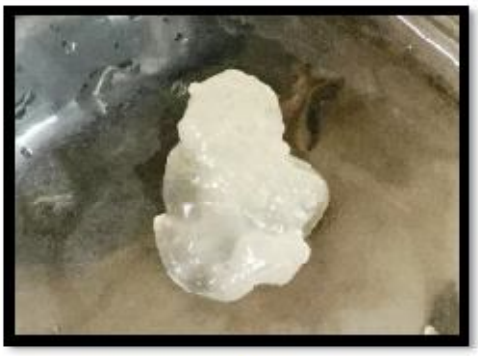
Further rise in temperature reported deswelling of hydrogel. This behaviour was absent in hydrogel with 6% AAm but comparably swelling rates were low i.e. 19.88% over rising temperature range of 20-50°C. AA and AAm both being hydrophilic can dissolve in water, their polymeric network of appropriate ratio can be helpful in absorbing water at high temperature. While PAA being anionic moiety will absorb water, PAM being viscous and gel like will assist it to retain a large volume. This statement is quite true as long as AAm content is below 4% of AA. Beyond this value reverse behaviour will be observed as investigated from current research.

***3.5 In vitro drug release***

From this experiment it was observed that at 40°C the drug release has taken place (**fig 5c**) and there was a slight increase in pH from 2.5 to 3.65 (measured by digital pH meter) of SGF observed within a span of 10 min. After complete delivery of drug the rupture in hydrogel structure was observed (**fig 5d**). Hydrogel with –COOH- group tend to swell when pH of solvent is more than pKa of ionic moiety itself [**11**]. Since –COOH- is a weak ionisable group and also with excess of AAm at low pH the hydrogel expels the antacid at 40°C to increase the acidity of SGF and exhibit therapeutic effect. With a slightly more appropriate composition of monomers, modification in properties by various reaction schemes and use of cross linker to raise the swell content of hydrogel this polymer can be utilised in achieving quick and effective drug delivery.

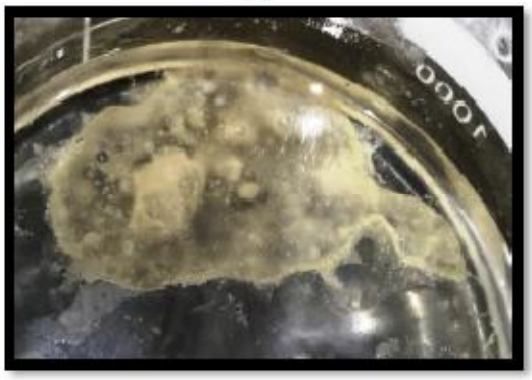
| | Swell content (g/g) of hydrogel with varying AAm amount | | | |
|---|---|---|---|---|
| **Temperature (°C)** | **1.5% AAm** | **2% AAm** | **4% AAm** | **6% AAm** |
| 20 | 0 | 0 | 0 | 0 |
| 30 | 0.1425 | 0.2220 | 0.1115 | 0.0644 |
| 40 | 0.2425 | 0.2420 | 0.1124 | 0.1047 |
| 50 | 0.2182 | 0.3047 | 0.0862 | 0.1988 |
| 60 | 0.1907 | 0.2549 | 0.0365 | 0.1756 |
| 70 | 0.1299 | 0.1916 | 0.0497 | 0.0775 |
| 75 | - | - | 0.0789 | 0.0629 |
| 80 | - | - | 0.0536 | 0.0596 |
| 85 | - | - | 0.0302 | 0.0096 |

**Table 2: Swell content of PAA-co-AAm at rising temperature varying AAm amount**

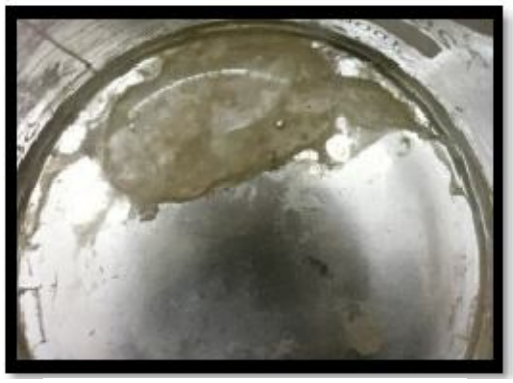


(a)

(b)



(c)



(d)

**Fig 5: In vitro drug release study. (a) Dry hydrogel, (b) Hydrogel loaded with Nexpro fast 20, (c) Drug expelled out of hydrogel in SGF, (d) Disintegration of hydrogel in SGF after drug release**

## CONCLUSION

Thermoresponsive and pH responsive PAA-co-AAm hydrogel was synthesised and studied for delivering stomach specific antacid. The swelling studies and kinetic studies were carried out by varying the AAm content of the hydrogel. It was concluded that hydrogel with AAm content of 4% showed desorption close to human body temperature. The purpose of this investigation was to determine the effect of AAm content on transition temperature of

PAA-co-AAm and the results were quite appreciable as not only did it resulted in tuning the transition temperature but also provided a hint about dual responsiveness of PAA-co-AAm i.e. at low temperature and high pH absorption of solvent or any fluid was predicted while at high temperature and low pH desorption was observed. While absorption behaviour can be beneficial in loading liquid drug, desorption behaviour can provide means to expel it out of the polymer matrix. In modern days stimuli responsive polymers can be thought of proving very beneficial as conventional drug delivery system does not focus on poor solubility of most of the drugs, cytotoxicity of certain drugs specific to anti cancer effect, target specific delivery of therapeutics and protection of oral drugs from fluctuating physiological environment (pH=7 within oesophagus, 1.5-3.5 within stomach and 6-7.4 within intestine) of human system. Also in current investigated a challenge still remain of lowering the transition temperature of PAA-co-AAm to expel the drug at 37°C, 3°C lower than its original transition temperature i.e. 40°C.

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