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SYNTHESIS AND CHARACTERIZATION OF ACRYLIC PHARMACEUTICAL POLYMERS IN ALKALINE MEDIUM FOR CONTROLLED DRUG DELIVERY SYSTEM

Sandeep Gaur*[1], Krishna Kumar Sharma[2], B.P.Yadav[3], Yogesh Barshiliya[4], Sumita Shukla[5]

[1]Department of Pharmaceutical Sciences, Shri Venkateshwara University, Gajraula, (U.P.)

[2]Department of Pharmacy, Bharat Institute of Technology, Distt- Meerut, (Uttar Pradesh) India.

[3]Department of Chemistry, Meerut College, Distt- Meerut (Uttar Pradesh) India.

[4]Venkateshwara School of Pharmacy, Distt- Meerut (Uttar Pradesh) India.

[5]Ravi Shankar College of Pharmacy, Distt- Bhopal (M.P)

Corresponding author's Email: sandipgaur@yahoo.com Mob no.-09719813241.

ABSTRACT:

The aim was to synthesized pH dependent polymers in different monomeric ratio, which were intended to be used for controlled drug delivery system. In this study we took monomers which were previously synthesized. i.e. Methylmethacrylate (MMA) and Acrylic Acid(AA) in different ratio (in moles) as follow-MMA:AA (0.7:0.3), MMA:AA (0.6:0.4), MMA:AA (0.5:0.5), MMA:AA(0.4:0.6) and MMA:AA (0.3:0.7) with solvent Tetrahyrdrofuran(THF) and Azobis-isobutyronitrile (AIBN) Initiator, which under goes polymerization. Polymers were prepared by solution polymerization technique and free radical mechanism. Swelling behavior of different polymeric films (polymers) which have obtained from polymerization in different monomeric ratios, studied in different pH buffer solutions. The different pH buffer solutions were Hydrochloric acid buffer pH 1.2, Hydrochloric acid buffer pH 2.0, Phosphate buffer pH 6.0, Phosphate buffer pH 7.4, Phosphate buffer pH 8.0.These different pH buffer solutions were prepared according to Indian Pharmacopoeia 2007.The changes in polymeric films in phosphate buffer (pH 8.0, pH 7.4) after 15,30, 45,60,75,90,120 minutes were noted. In buffer (pH 6.0, pH2.0, and pH 1.2) the changes were noted after 1 hour,2hours,2 days,3 days,4 days,5 days,6 days,7 days. Swelling ratio calculated by formula. For microencapsulation paracetamol drug was taken as a model drug. Emulsification solvent evaporation method have used for micro encapsulation of model drug. The standard calibration curve of paracetamol obtained a straight line. The relation between drug concentration & absorbance measured at 249 nm found linear. The standard calibration curve obeys Bear's Lambert law within the concentration range of 0.0005mg/ml to 0.00003mg/ml. The drug was estimated by UV spectrophotometer at 249 nm using a calibration curve based on standard solutions. The percentage of paracetamol encapsulated with respect to total amount of paracetamol encapsulation taken loading efficacy. In vitro dissolution release of paracetamol from micro spheres was evaluated using paddle dissolution apparatus (Lab India Disso 2000 dissolution tester). Dissolution media was 900 ml phosphate buffer (pH 7.4) & to this media the microspheres containing 200 mg of paracetamol were added. The system was stirred at 500 pm & temp at 37^{o}C± 0.5 ^{o}C . Samples were drawn at specified time intervals (10 min, 20 min, 30 min, 40 min, 50 min & 60 min) filtered & assayed spectrophotometrically at 249nm. For swelling study, all the copolymers in different monomeric ratio did not show good swelling or dissolution characteristic in acidic pH (pH 1.2-pH6.0) methylmethacrylate: acrylic acid with monomer ratio 3:7 completely dissolved within 2 hours.

Keywords: Polymers, Methylmethacrylate, Acrylic acid, Ultraviolet Spectrophotometer, Dissolution apparatus.

INTRODUCTION

The Stone Age was the first and was followed by the Bronze, Iron, and steel Ages and now we are in the age of polymers. It is a time in which synthetic polymers are the material of choice for a large variety of industrial and domestic applications. The large number of current and future applications of polymeric materials has created a great national need for persons specially trained to carry out research and development in polymer science and engineering (Marye Anne Fox et al., 1998). Polymers (having many parts), Johan JaKob Berzelius introduced this term in 1830.since most of the functional groups present are carboxylic acid esters, thus quite logically, these macromolecules belong to the class of polymers known as polyesters(John Olmsted III et al.,1997). A typical polymer consists of more than 10,000 atoms. Macromolecules are so common in everyday life that people hardly notice their presence. Chemists have learned how to manufacture macromolecules in the lab, but nature masters the techniques eons ago. At the beginning of 20^{th} century the chemistry of large molecules was unknown and their synthesis was definitely unthinkable. A German scientist named Hermann Staudinger proposed in the 1920s that it is possible to have large molecules which were made up of many thousands of atoms. Rubber and Bakelite were actually many small molecules which were held together by an unknown force (Andrew J. Peacock et al., 2012). Polymers (Greek-POLY…many and MEROS…parts) are macromolecules made up of repeating units called 'monomers' joined by the same type of linkage. The suffix in polymer 'mer' is originated from Greek word *meros* – which means part. The word polymer is thus coined to mean material consisting of many parts/mers. Most of the polymers are basically organic compounds, however they can be inorganic. e.g. silicones based on Si-O network(Gordon et al.,1998).

A new applications for polymers were found, researchers started to investigate their applications in pharmaceutical sectors. Polyglycolic acid (PGA) was such a polymer, used in surgical sutures by surgeons .Scientists also found a method to implant drug bearing polymer wafers after brain surgery, were the polymers could slowly release drugs at specific targeted organ or tissue in the body(Jeremy Robinson et al., 2001). Polymer scaffolds were also developed to grow cells; this was a big improvement over growing cells in flat plates, which prevented them from producing the normal array of proteins.

Advancement in modern polymer technologies such as photo-electronics, pharmaceutical and biomedical fields, environmental biodegradable systems and specific composites are increasingly interrelated. The interdisciplinary feature of the achievement provides unusual solutions for various technologies of advanced polymer systems and initiate further research activities. Thus development of an area of advanced polymer systems is adapted to another much sooner than earlier (Srikanth Pilla, 2011). Polymers already have a range of applications that far exceeds that of any other class of material available to man. Polymer uses are being developed in such diverse areas as: conduction and electricity, heat and light, molecular based information storage and processing, molecular composites, unique separation membranes, revolutionary new forms of food processing and packaging, health, housing, and transportation. Polymeric materials have a vast potential for exciting new applications in the foreseeable future (Gordon et al.,1999). In Agriculture and Agribusiness polymeric materials are used in and on soil to improve aeration, provide mulch, and promote plant growth and health (L. O. Ekebafe et al., 2011). Many biomaterials, especially heart valve replacements and blood vessels, are made of polymers like Dacron, Teflon and polyurethane (Jeremy Robinson et al., 2003). Plastic containers of all shapes and sizes are light weight and economically less expensive than the more traditional containers. Clothing, floor coverings, garbage disposal bags, and packaging are other polymer applications (R.J. Young Chapman et al., 1987). Industry Automobile parts, windshields for fighter

planes, pipes, tanks, packing materials, insulation, wood substitutes, adhesives, matrix for composites, and elastomers are all polymer applications used in the industrial market (Charles G. Gebelein,1985). Sports Playground equipment, various balls, golf clubs, swimming pools and protective helmets are often produced from polymers (J.M.G. Cowie, 1991). The application of polymeric materials in medicine is a fairly specialized area with a wide range of specific applications and requirements (Quirk R, 2003). Although the total volume of polymers used in this application may be small compared to the annual production of polyethylene, for example, the total amount of money spent annually on prosthetic and biomedical devices exceeds $16 billion in the United States alone (Peppas N et al., 1994).These applications include over a million dentures, nearly a half billion dental fillings, about six million contact lenses, over a million replacement joints (hip, knee, finger, etc.), about a half million plastic surgery operations (breast prosthesis, facial reconstruction, etc.), over 25,000 heart valves, and 60,000 pacemaker implantations. In addition, over 40,000 patients are on hemodialysis units (artificial kidney) on a regular basis, and over 90,000 coronary bypass operations (often using synthetic polymers) are performed each year (Clayden J. et al., 2000). No one working in the pharmaceutical sector can be unaware of type continuing and increasing use of synthetic polymers in all fields of pharmacy. In 1950s, synthetic organic polymers were first used as ion exchange resins for the separation of pharmaceutical products (Florence et al., 1984). In 1970s, Yolles and coworkers demonstrated that a lactic acid based polymer could be used for controlled drug delivery of steroids, thus opening grounds for the existing fields of polymeric drug delivery. The hydrophilic, hydrophobic or pH sensitive polymers have been used in oral dosages forms for several decades to sustain or delay release of the drug or otherwise improve the formulation (Kopecek J, 1988). Polymeric materials used in drug delivery are incorporation of chemicals and drugs into polymeric materials can allow the transport and delivery of substances through hostile environments to specific sites. Additional functionality can then incorporated by using responsive polymers which can be triggered by a change in pH, pressure, temperature or light to release the active components that they carry. This invention generally relates to biodegradable polymers useful as carriers of pharmaceutical compounds and as degradation agents. Low molecular weight polymers tend to degrade quickly while, High molecular weight carriers take a long time to degrade and be cleared from the body (V. R Gowariker et al., 1986).

Polymers carriers have several advantages over other delivery methods such as liposomes and antibodies. Liposomes are taken up by macrophages in the liver and spleen and stealth liposomes have other side effects. Antibodies have the disadvantages that most receptors on tumor cells are also present on normal cells, making it hard to find ones that are unique to cancer.[19] Another advantage of polymers is that the linkage can be designed to control where and when the drug is released However, polymer carrier systems also have their disadvantages compared to liposomes, which are basically empty vesicles that can be “stuffed full of drug” Polymer have a low drug - carrying capacity (Branon et al., 1997).

Controlled drug delivery occurs when a polymer is judiciously combined with a drug or active agent in such a way that the active agent is released from the material in a pre designed manner (Islamova et al., 2006). `The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize (Park et al., 1997).With traditionally tablets or injections, the drug level in the blood rises after each administration of the drug and then decreases until the next administration. In controlled drug delivery systems the drug level in the blood remains constant, between the desired maximum and minimum, for an extended period of time. Depending on the formulation and the application, this time may be anywhere from 24 hours (Procardia XL) to

1 month (Lupron Depot) to 5 years (Norplant). In recent years controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled release systems can respond to changes in the biological environment and deliver-or cease to deliver – drugs based on these changes. Polymers are becoming increasingly important in the field of drug delivery (Veeran Gowda Kadajji et al., 2011).

The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics (Sinha VR et al., 1988). Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules of many useful properties. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it (Mathiowitz E et al., 1999). The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. The technique of microencapsulation depends on the physical and chemical properties of the material to be encapsulated (Jackson L.S et al., 1991). The reasons for microencapsulation in some cases, the core must be isolated from its surrounding, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of sticky materials, or isolating a reactive core from chemical attack(Pongpaidal Y et al., 1994). In other cases, the objective is not to isolate the core completely but to control the rate at which it leaves the microcapsules, as in the controlled release of drugs or pesticides (Partricil B et al., 2010). The problem may be as simple as masking the taste or odour of the core, or as complex as increasing the selectivity of an adsorption or extraction process.

MATERIAL AND METHODS:

Various chemical and reagents used during synthesis of polymers like Acrylic Acid (Thomas Baker), Azobis-iso butyronitrile (Merck), Chloroform(Merck), Hydroquinone (Qualigens), Methyl methacrylate(Merck), Methanol(Rankem), Petroleum Ether(Rankem), anhydrous Sodium Sulphate (Qualigens), Potassium chloride (Rankem), Hydrochloric acid(Qualigens), Potassium hydrogen Phthalate(Merck), Sodium Hydroxide(Rankem), Potassium dihydrogen phosphate(Qualigens), Boric acid(Rankem), Dichloromethane(Merck), Potassium chloride(Merck) and Acetone(Merck).

Purification of monomers

Monomers which are previously synthesized (i.e.; Methyl methacrylate) and acrylic acid were distilled under vacuum 100 ml of monomer is taken in the RBF and 1 gm of hydroquinone (as polymerization inhibitor) was added to it. This mixture was heated for 1hr at 40^{o}C then distilled off under reduced pressure of 15 mbar. This reaction mixture was distilled at 99^{o}C & purified monomers were collected on an ice bath & stored in refrigerator.

Polymerization

Polymers were prepared by using solution polymerization technique and mechanism involved is free radical mechanism. The polymers were prepared in a test tube, 5 ml THF (as a solvent) and AIBN (as initiator) and specific molar quantities of monomers as mentioned in table (1) was taken. This mixture was agitated properly for 5 min, and then N_2 gas was slowly purged to this reaction mixture for 5 min and was kept in thermostat water bath at 65^{0} C over

night (15-16 hrs). After 15-16 hrs the polymer was synthesized, this was in solution form. The precipitated polymers were dried at room temperature and stored. MMA & AA were used in combination for polymerization.

Swelling studies of polymers in different pH.

For swelling studies, in different pH buffer solutions i.e; Hydrochloric acid buffer pH 1.2, Hydrochloric acid buffer pH 2.0, Phosphate buffer pH 6.0, Phosphate buffer pH 7.4, Phosphate buffer pH 8.0.These different pH buffer solutions were prepared according to Indian Pharmacopoeia 2007. Films of above polymers were prepared. For swelling studies, 15 ml of each of the above buffer was taken in four different test tubes for each polymer. Approximately 5-6 mm^2 in size and 10-15 mg in weight polymeric films were placed in each test tube. The changes in films in phosphate buffer (pH 8.0, and pH 7.4), after 15, 30, 45, 60, 90,120 minutes were noted (table 1, 2). In buffer (pH 6.0, pH2.0,and pH 1.2) the changes were noted after 1 hour,2 hour, 2days,3 days,4 days,5 days,6 days,7 days(table 3,4,5).Swelling ratio(Q) was calculated by the formula: W_w-$W_D/W_D \times 100$. Where W_D=Dry (initial) weight of polymeric film (mg), Ww (final) weight of polymeric film (mg).

Microencapsulation of model drug

Paracetamol (Malidens650) drug was taken as model drug for microencapsulation. 100 mg of microspheres crushed & totally dissolved in a 100 ml solution containing 1 volume phosphate buffer (pH 7.4) & 1volume methanol & further diluted with buffer. The drug was estimated by UV spectrophotometer at 249 nm using a calibration curve based on standard solutions. The percentage of Paracetamol encapsulated with respect to total amount of Paracetamol encapsulation taken loading efficacy.

In vitro dissolution release of Paracetamol from micro spheres was evaluated using paddle dissolution apparatus. Dissolution media was 900 ml phosphate buffer (pH 7.4) & to this media the microspheres containing 200 mg of Paracetamol were added. The system was stirred at 500 pm & temp at $37^oC \pm 0.5\ ^oC$ samples were drawn at specified time intervals (10 min, 20 min, 30 min, 40 min, 50 min & 60 min) filtered & assayed spectrophotometrically at 249nm.

RESULT AND DISCUSSION:

We took monomer in combination i.e. methylmethacrylate (MMA) & Acrylic acid(AA) in different ratio molar quantities the percentage yield as follow- MMA(0.7): AA(0.3) Polymer yield 4.38 gm (97.10 %), MMA(0.6) : AA(0.4) 3.06 gm(93.6%), MMA(0.5) : AA(0.5) polymer yield 4.70gm (92.67%) MMA (0.4): AA (0.6): polymer yield 3.98 gm (97.3%), MMA (0.3): MA (0.7) yield5.37 gm (96.38%).

Synthesized copolymers were screened for swelling & dissolution behavior in pH1.2, pH 2.0, pH 6.0, pH 7.4 & pH 8.0. It was expected that copolymer should be solubilized with in the desired time in alkaline pH buffers (7.4 & 8.0), but do not in acidic buffers (pH 1.2 - pH 6.0) due to presence of acidic groups.

From the swelling study it was observed that the copolymer of methylometnacrylate : acrylic acid with monomeric ratio 7:3, 6:4 & 5:5 did not dissolved into the basic buffer due to low acidic monomer content. Whereas copolymer methyl methacrylate : acrylic acid with monomeric ratio 4:6 shows good swelling characteristic but do not dissolved completely within the desired time. The copolymer methylmethacrylate: acrylic acid with monomer 3:7 completely

dissolved with in 2 hrs. The copolymer with monomeric ratio 3:7 dissolved maximum within the desired time. The drug (Paracetamol) content in the microspheres of copolymer MMA (0.3): AA (0.7) Paracetamol percentage loading 41% & loading efficiency 33.33%. Microspheres showed in basic media release about 60% within 30 min & 95%with in 1 hour. Which is explained the curve plotted between percentage release v/s time (figure A). All the copolymers did not show good swelling or dissolution characteristic in acidic pH (1.2, 2.0, and 6.0).

Table (1) Swelling Studies in Phosphate Buffer pH 8.0

Polymers	W_D (mg)	W_W Q	15 min	30 min	45 min	60 min	75 min	90 min	120 min
MMA(0.7) AA(0.3)	10	W_W	16	15	16	15	17	18	20
		Q	60	50	60	50	70	80	100
MMA(0.6) AA(0.4)	16	W_W	18	20	22	24	26	22	18
		Q	12.5	25	37.5	50	62.5	37.5	12.5
MMA(0.5) AA(0.5)	14	W_W	15	17	17	15	14	13	10
		Q	7	21	21	7	0	-7	-28
MMA(0.4) AA(0.6)	14	W_W	17	17	15	15	13	12	8
		Q	21	21	7	7	-7	-14	-35
MMA(0.3) AA(0.7)	15	W_W	15	13	11	9	7	Dissolved	
		Q	0	-13	-27	-39	-50		----

The values given in brackets are molar quantity of monomers.

Table (2) Swelling Studies in Phosphate Buffer pH 7.4

Polymers	W_D (mg)	W_W Q	15 min	30 min	45 min	60 min	75 min	90 min	120 min
MMA(0.7) AA(0.3)	14	W_W	17	15	17	16	18	18	20
		Q	21	7	21	14	28	28	42
MMA(0.6) AA(0.4)	13	W_W	15	19	19	20	20	21	22
		Q	15	46	46	54	54	62	69
MMA(0.5) AA(0.5)	15	W_W	16	18	20	20	19	17	14
		Q	6	18	30	30	25	13	-7
MMA(0.4) AA(0.6)	12	W_W	14	15	13	11	100	9	7
		Q	16	24	8	-8	-16	-24	-40
MMA(0.3) AA(0.7)	12	W_W	14	14	12	10	9	Dissolved	---
		Q	16	16	0	-16	-24		

The values given in brackets are molar quantity of monomers.

Table (3) Swelling Studies in Phosphate Buffer pH 6.0

Polymers	W_D (mg)	W_W Q	1 Day		2 Day	3 Day	4 Day	5 Day	6 Day	7 Day
			1 Hour	2 Hour						
MMA(0.7) AA(0.3)	4	W_w	18	18.6	20	21	18	17	16	15
		Q	27	30	34	32	26	29	24	22
MMA(0.6) AA(0.4)	12	W_W	12	13.3	16	17	14.9	13.6	12.5	12
		Q	-11	-8.5	-6	-11	-7	-11	-12	-8
MMA(0.5) AA(0.5)	16	W_W	13.5	14	16	17	15.3	15	14	14
		Q	-9	-11	-15	-13	-4	2	3	4
MMA(0.4) AA(0.6)	15	W_W	11	9.6	11	11.2	10.2	9.6	9	10
		Q	-8	-12	-20	-21	-27	-28	-28	-26.4
MMA(0.3) AA(0.7)	15.4	W_W	16	18	21.6	23	22.5	21	18.7	18
		Q	11	16	29	40	36	23	12	5.3

The values given in brackets are molar quantity of monomers.

Table (4) Swelling Studies in Phosphate Buffer pH 2.0

Polymers	W_D (mg)	W_W Q	1 Day		2 Day	3 Day	4 Day	5 Day	6 Day	7 Day
			1 Hour	2 Hour						
MMA(0.7) AA(0.3)	12	W_W	13.5	13.2	13	11.8	11	11.5	11	12
		Q	16	8	8	0	0	0	-6	0
MMA(0.6) AA(0.4)	14	W_W	14	16	15	16	16	15	12	12
		Q	0	14	7	14	14	7	-7	0
MMA(0.5) AA(0.5)	14	W_W	18	18	17	17	17	15	16	15
		Q	26	28	21	21	21	7	14	7
MMA(0.4) AA(0.6)	15	W_W	17.3	18	20	20	17	18	18	16.7
		Q	13	20	32	32	13	20	20	13.5
MMA(0.3) AA(0.7)	15	W_W	16	19	21	21.5	19	18.7	17	17.3
		Q	13.6	25	32	36	25	20	13	13.4

The values given in brackets are molar quantity of monomers

Table (5) Swelling Studies in Phosphate Buffer pH 1.2

Polymers	W_D (mg)	W_W Q	1 Day		2 Day	3 Day	4 Day	5 Day	6 Day	7 Day
			1 Hour	2 Hour						
MMA(0.7) AA(0.3)	12	W_W	14	13	13	12	12	12	11	12
		Q	16	8	8	0	0	0	-8	0
MMA(0.6) AA(0.4)	14	W_W	14	16	15	16	16	15	13	14
		Q	0	14	7	14	14	7	-7	0
MMA(0.5) AA(0.5)	14	W_W	18	18	17	17	17	15	16	15
		Q	28	28	21	21	21	7	14	7
MMA(0.4) AA(0.6)	15	W_W	17	18	20	20	17	18	18	17
		Q	13	20	32	32	13	20	20	13
MMA(0.3) AA(0.7)	15	W_W	17	19	20	21	19	18	17	17
		Q	13	25	32	36	25	20	13	13

The values given in brackets are molar quantity of monomers.

Drug Content of Microspheres

The drug content in microspheres of co polymer MMA (0.3): AA (0.7) follows as:-

Paracetamol (%) loading = 40.0%

Loading Efficiency (%) = 32.30%

In Vitro release study for microspheres

The microspheres prepared were showed as release in basic media of about 60% within the 30 min and 95% within the 1 hour as shown in the curve plotted between percentage releases v/s time (figure 1).

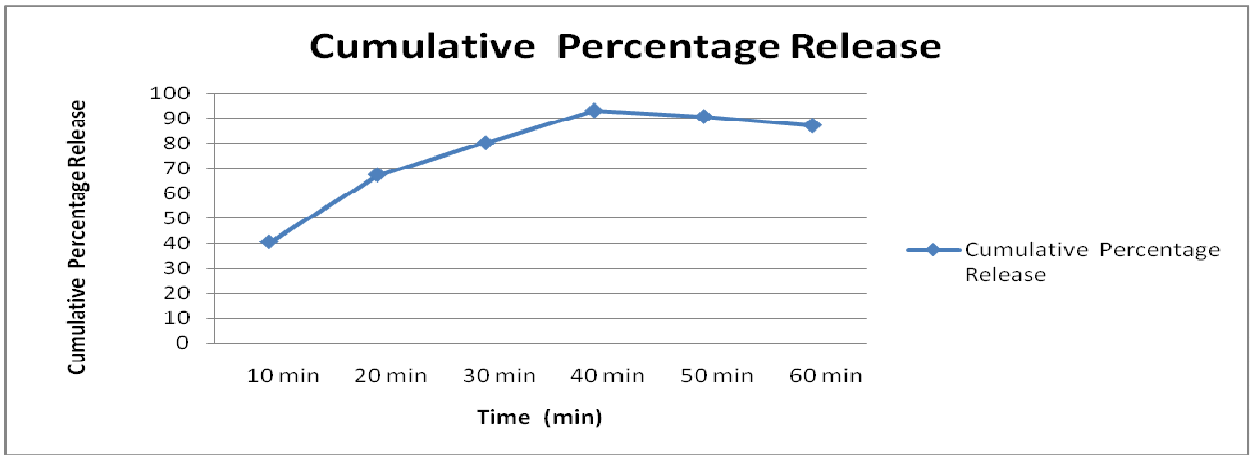

Figure:1 Cumulative percentage release

CONCLUSION:

In the present work, pH sensitive, biodegradable copolymers have been developed by free radical polymerization using Azobis-iso butyronitrile (AIBN) as an Initiator. The copolymer with monomeric ratio 3:7 dissolved maximum within the desired time. It was observed that swelling was also increased at higher pH due to availability of more ionized carboxylic group of acrylic acid. The result confirms that the copolymers methylmethacrylate(MMA): acrylic acid(AA) with the ratio 3:7 can play an important role in oral pharmaceutical formulations as film coating agents or in controlled release drug delivery system.

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