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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF SWELLING BEHAVIOR OF PHARMACEUTICAL POLYMERS IN DIFFERENT pH FOR CONTROLLED DRUG DELIVERY SYSTEMS

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ABSTRACT:

The pharmaceutical industry is evaluating modes of delivery for their prized therapeutics at every step of the design cycle. In recent years, pH dependent drug delivery systems have focused much for specific purposes. Synthesis of pH dependent polymer in different monomeric ratio was intended to be used for controlled drug delivery systems. Previously synthesized monomers i.e; ethyl methacrylate (EMA) and acrylic acid (AA)took in different monomeric ratio (in moles) as - EMA:AA(0.7:0.3), EMA:AA (0.6:0.4), EMA:AA (0.5:0.5),EMA:AA(0.4:0.6) and EMA:AA(0.3:0.7) with solvent Tetrahyrdrofuran(THF) and Azobis-iso butyronitrile (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 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) ethylmethacrylate : acrylic acid with monomer ratio 3:7 completely dissolved within 2 hours.

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

INTRODUCTION

Polymers are macro molecules made up of repeating units called "monomers" joined by the same type of linkage. Starch cellulose & rubber all possesses polymeric properties. Man made polymers have been studied since 1832. We are surrounded by polymers every day, every where.[1] We wear clothes containing polyester & nylon fibers, food packaged in polyethylene container, pipe, walk on carpets made of polyolefin & sleep on mattresses made of poly urethane foam. Polyglycolic acid (PGA) was such a polymer, used in surgical sutures by surgeons.Many biomaterials, especially heart valve replacement & blood vessels are made of polymers like Dacron, Teflon & polyurethane. In 1950, synthetic organic polymers were first used as ion exchange resins for the separation of pharmaceutical products .

Polumeres (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.[2] 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. All living cells produce a complex array of different types of macromolecules. Plants and animals contain a rich variety of biochemical macromolecules.[3] 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).[4] Synthetic polymers are of increasing interest in drug delivery as therapeutic agent. Polymers show usually an improved pharmacokinetics compared to small molecule drugs with longer circulation time and the potential for tissue targeting. Synthetic polymers are being used as drug delivery systems as a

polymeric drug itself or in combination with small molecule drugs or with bio macromolecules such as proteins and poly (nucleic acids).[5]

In 1970, yolles & coworker demonstrated lactic acid based polymer used for controlled drug delivery of steroids, opening grounds for the exciting fields of polymeric drug delivery. Controlled drug delivery occurs, when a polymer is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. [6] In controlled drug delivery systems designed for long term administration the drug level remaining constant, between the desired maximum & minimum, for an extended period of time. Pharmaceutical applications of polymers range from their use as binders in tablets to viscosity & flow controlling agents in liquids, suspensions & emulsions polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability & to modify drug release characters. Advantages of controlled release devices possibly include delivery to the required site, delivery at the required rate, reduced dangers of overdose or Side effects. [7,8]

Microcapsules are a small sphere with a uniform wall around it. Most microcapsule has diameters b/w a few micro meters & a few millimeters.[9] Micro-encapsulations can be used to slow release of a drug into the body. This may permit one controlled release dose to substitute for several doses of non-encapsulated drug & also may decrease toxic side effects for some drug & by preventing high initial concentration in the blood, morphology of polymer matrix play an important role in governing the release characteristic of the encapsulated drug.[10] Polymer matrix could be formulated as micro/nanospheres, gel film or an extruded shape. The shape of extruded polymer can be important to the drug release kinetics. Zero order kinetics be achieved using a hemispherical polymer form. Polymeric drug delivery products can be formulated with excipients added to the polymer matrix.[11] The main objective of having excipients in the polymer either to modulate the drug release or to stabilize the drug or to modulate the polymer degradation kinetics[12].

Enteric coatings consist of pH sensitive polymers which are unionized at low pH (in stomach); at high pH (in intestine) the polymers ionize causing swelling, or dissolving of the polymer. Formulation that can not the rate & period of drug delivery & target specific areas of the body treatment become increasingly & complex.[13]

Challenges to not only development of new treatments but also the mechanism with which to administer them.[14] Therapeutic uses of a drug carrier system have significant impact on the treatment & potential cure of many chronic diseases, including cancer, diabetes mellitus, Rheumatoid arthritis, HIV infection & drug addiction.

MATERIAL AND METHODS:

Materials

Various chemical and reagents used during synthesis of polymers like Acrylic Acid (Thomas Baker), Azobis-iso butyronitrile (Merck), Chloroform(Merck), Hydroquinone (Qualigens), Ethylmethacrylate(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 and polymerization of monomers

Monomers which are previously synthesized i.e.; Ethylmethacrylate and acrylic acid were distilled under vacuum with 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.

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. EMA & AA were used in combination for polymerization.

Swelling studies of synthesized 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 7.8, 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 7.4, and pH 8.0), 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 × 100. Where W_D=Dry (initial) weight of polymeric film (mg), Ww (final) weight of polymeric film (mg).

Microencapsulation of model drug

Paracetamol (Ranbaxy pharmaceutical Ltd) 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°C± 0.5 °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.

RESULT AND DISCUSSION

We took synthesized monomer in combination i.e. ethylmethacrylate (EMA) & Acrylic acid(AA) in different ratio molar quantities the percentage yield as follow- EMA(0.7): AA(0.3) Polymer yield 4.91 gm (98.45 %), EMA(0.6) : AA(0.4) 3.47 gm(96.96%), EMA(0.5) : AA(0.5) polymer yield 5.90gm (94.81%), EMA (0.4): AA (0.6): polymer yield 4.33 gm (99.12%), EMA (0.3): MA (0.7) yield 4.43 gm (99.03%).

Synthesized copolymers were screened for swelling & dissolution behavior in pH1.2, pH 2.0, pH 6.0, pH 7.4 & pH 8.0 (table 1,2,3,4, and table 5). 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 ethylmethacrylate : 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 ethylmethacrylate : acrylic acid with monomeric ratio 4:6 shows good swelling characteristic but do not dissolved completely within the desired time. The copolymer ethylmethacrylate: 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 1.2

Polymers	W_D		1 Day		2 Day	3 Day	4 Day	5 Day	6 Day	7 Day
			1 Hour	2 Hour						
EMA(0.7) AA(0.3)	16	W_W	19	22	22	21	19	19	18	17
		Q	19	37.5	37.5	31	19	19	12.5	6.3
EMA(0.6) AA(0.4)	13	W_W	15	17	18	20	19	20	19	18
		Q	15	30	37.5	54	46	54	46	37.5
EMA(0.5) AA(0.5)	14	W_W	16	17	19	20	200	19	21	19
		Q	14	21	35	42	42	35	49	35
EMA(0.4) AA(0.6)	14	W_W	14	15	17	17	19	18	17	15
		Q	0	7	21	21	35	28	21	7
EMA(0.3) AA(0.7)	16	W_W	16	16	17	16	18	17	18	18
		Q	0	0	6.3	0	12.6	6.3	12.6	12.6

The values given in brackets are molar quantity of monomers.

Table 2: Swelling Studies in Phosphate Buffer pH 2.0

Polymers	W_D		1 Day		2 Day	3 Day	4 Day	5 Day	6 Day	7 Day
			1 Hour	2 Hour						
EMA(0.7)		W_W	19	22	22	21	19	18.5	18	17
AA(0.3)	16	Q	19	37.5	37.5	31	19.5	19	12.5	6.3
EMA(0.6)		W_W	14	16	17	21	19	20	19	18
AA(0.4)	13	Q	13.6	28	35	51	46	54	46	37.5
EMA(0.5)		W_W	15	16.5	18	19	26	21	20.5	18
AA(0.5)	14	Q	13	20	33	40	40	32	47	33
EMA(0.4)		W_W	11	14	16	16.8	19.3	18.6	16	15.7
AA(0.6)	14	Q	0	8	23	24	32	26	20.5	7.7
EMA(0.3)		W_W	14	15	16	16	16	17	17	17
AA(0.7)	16	Q	0	0	4.8	1	11	6	11.5	12

The values given in brackets are molar quantity of monomers.

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Table 3: Swelling Studies in Phosphate Buffer pH 6.0

Polymers	W_D		1 Day		2 Day	3 Day	4 Day	5 Day	6 Day	7 Day
			1 Hour	2 Hour						
EMA(0.7)		W_W	17	17.8	21.1	23.2	20	18.2	16.2	15
AA(0.3)	14	Q	13.5	14.8	29	35	28	16	11	2
EMA(0.6)		W_W	13	13.6	17.8	17	16	14	14	11
AA(0.4)	12	Q	21	32	31	24	35	15	31	22
EMA(0.5)		W_W	8	9	12.4	13.8	14	12	12	13
AA(0.5)	11.1	Q	11.5	13.5	21	29	41	36	26	25.3
EMA(0.4)		W_W	12.1	13	14.1	15	16	13	12	11
AA(0.6)	11.4	Q	1	3.5	6	12	8	-3	-10	-8
EMA(0.3)		W_W	13.3	14.7	16.5	18.2	16.5	13	13	12
AA(0.7)	16	Q	-4.2	3.5	11	2	-3	-5	-8	-10

The values given in brackets are molar quantity of monomers.

Table 4: 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
EMA(0.7)		W_W	14	16	16	15	19	20	23
AA(0.3)	14	Q	0	14	14	7	36	43	63
EMA(0.6)		W_W	15	17	18	20	22	22	25
AA(0.4)	15	Q	0	13	18	31	44	44	68
EMA(0.5)		W_W	15	17	17	18	18	20	17
AA(0.5)	14	Q	7	21	21	28	28	43	21
EMA(0.4)		W_W	9	10	9	9	8	7	6
AA(0.6)	9	Q	0	11	0	0	-11	-22	-33
EMA(0.3)		W_W	16	16	15	14	13	10	
AA(0.7)	15	Q	6	6	0	-6	-12	-41	Dissolved

The values given in brackets are molar quantity of monomers.

Table 5: 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
EMA(0.7)		W_W	16	19	19	21	24	26	28
AA(0.3)	14	Q	6	26	26	40	60	73	86
EMA(0.6)		W_W	15	15	17	18	20	200	24
AA(0.4)	15	Q	7	7	21	28	42	42	70
EMA(0.5)		W_W	12	13	14	10	9	8	7
AA(0.5)	14	Q	0	8	16	-16	-24	-32	-40
EMA(0.4)		W_W	15	16	14	12	10	8	7
AA(0.6)	9	Q	0	6	-6	-18	-30	-39	-52
EMA(0.3)		W_W	11	11	100	8	7	5	
AA(0.7)	15	Q	0	0	-9	-27	-36	-54	Dissolved

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 = 41.0%

Loading Efficiency (%) = 33.33%

In Vitro release study for microspheres

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

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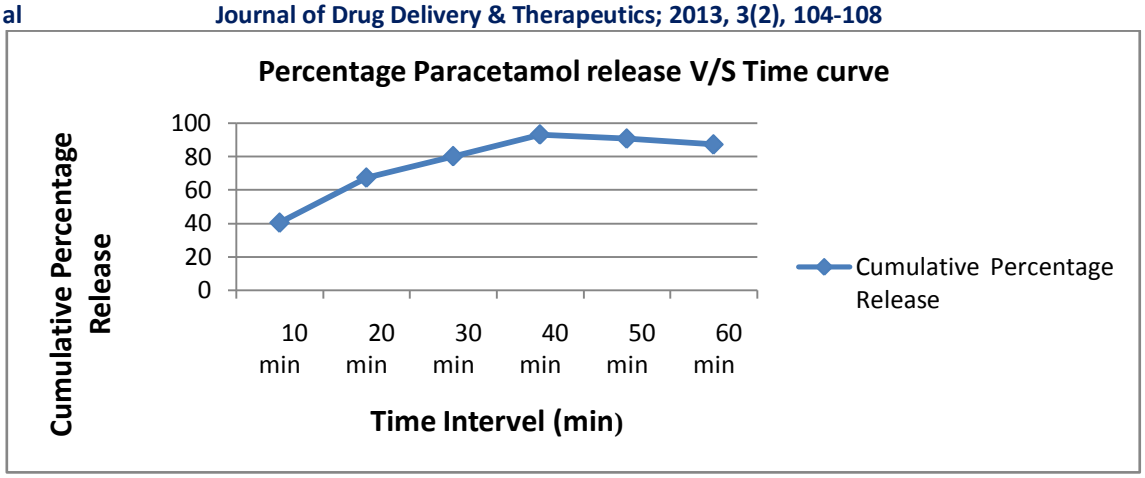

Figure 1: In vitro release of Drug from Microspheres

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 ethylmethacrylate(EMA): 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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