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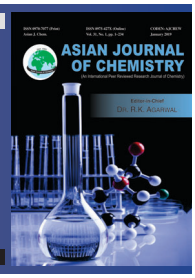

Preparation and Characterization of New Carrier Drug Polymers Based Maleimide and Its Drug Release Behaviour

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In this work, two new drug substituted monomers and new homogenous and heterogeneous polymers were synthesized loaded with medicinal properties to extend the controlled drug. The first step includes preparation of compound (**F1**) *via* reaction of maleic anhydride with 4-aminobenzoic acid. Then compound (**F1**) was converted to its corresponding acyl chloride derivative which reacted with amino drugs (sulfadiazine, chlordiazepoxide) afforded (**F2** and **F3**) monomers. Homogeneous polymers (**F8** and **F9**) prepared through polymerization reaction of free radicals of the monomers (**F2** and **F3**) under nitrogen using methyl ethyl ketone peroxide (MEKP) as initiator. Heterogeneous polymers (**F14** and **F15**) prepared through polymerization reaction of free radicals of the monomers (**F2** and **F3**) separately with acrylic acid under nitrogen using methyl ethyl ketone peroxide (MEKP) as initiator. All these prepared monomers and polymers were characterized by FT-IR and ^{1}H NMR, ^{13}C NMR spectroscopies. Controlled drug release and swelling % was studied in different pH values at 37 ºC. Intrinsic viscosities were measured at 25 ºC with Ostwald viscometer and applied the characteristic of solubility for these polymers.

Keywords: Maleimide, Copolymer, Sulfadiazine, Chlordiazepoxide, Drug delivery system.

INTRODUCTION

The functional polymers used in medicinal applications have attracted a great attention, which includes several applications such as artificial organs, tissue engineering, medical devices, dentistry, *etc*. [1,2]. The field of identification of polymers used as therapeutic agents and pharmacological properties for these polymers, therefore can be useful as carriers for small molecules or macromolecules like proteins [3]. The synthetic polymers with biological materials can also be positive and eligible [4,5].

Drug delivery systems are used for improving the therapeutic efficiency and safety of drugs by delivering them over the period of treatment to the site of action. Drug delivery systems may reduce the quantity and number of doses, biological inactivation and their side-effects [6]. Both non-degradable and biodegradable polymers used as prodrug depends on two forms injectable and implants systems [7-10]. Carrier system which be consider ideal for used in intravascular systems is circulation of blood stream, blood-compatible, avoid excretion in kidneys and target area, desired rate and degrade *in vivo* during or after drug release [11-13].

Basically bioactive polymers have temendrous benefits due to their high molecular weight and their compatibility, therefore polymers appears to have many advantages over low molecular weight agents as therapeutic agents [14-16]. The advantages aslo include higher specificity of action, improved the activity due to their interactions and lower toxicity [17].

Some properties like issue of polydispersity in molecular weight and structural heterogeneity which make the development of process more complicated [18,19]. Higher molecular weight and potentially limited of pharmacological properties of polymers can be utilized to design and develop therapeutic agents for disease situations, while the drugs with low molecular weight have unsuccessful to produce therapeutic profiles [20]. This work focused on the preparation of *N*-substituted maleimide based polymeric drugs to enhance the bioactivity of the drug by the combination of polymer. In order to examine the probab-

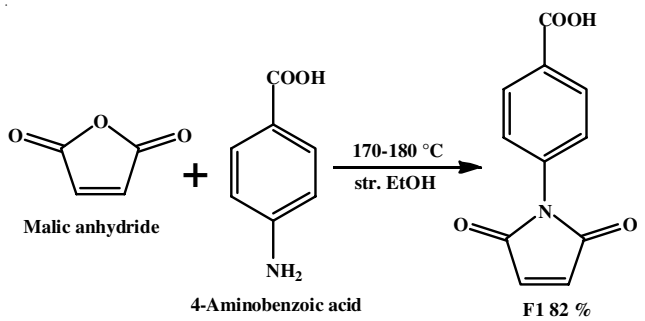
ility of getting best polymer based drugs using *N*-substituted maleimide, we reported the preparation of *N*-[5-benzoic maleimide] monomer and its polymerization and co-polymerization with acrylic acid. The spectral, thermal and physical properties have been studied to characterize the homo and co-polymers.

EXPERIMENTAL

All the chemicals used in this work were of analytical grade. The density of prepared polymers determined at 25 ºC by single stem pycnometer using displacement method [15] using water as a non-solvent. The measurements of intrinsic viscosity [η] were carried out in acetone at 30 ºC using an Ostwald viscometer suspended level viscometer. The FTIR spectra measurements were recorded using Fourier Trans Infrared Spector Promoter -Shimadzu within range (4000-400 cm-1). ^{1}H NMR spectra were recorded at 300 MHz in DMSO-d_6 on a VXR-300 spectrometer while ^{13}C NMR spectra were recorded at 75 MHz in DMSO-d_6 on Bruker-300A spectrometer.

Synthesis of compound (F1): 4-Aminobenzoic acid (0.7 g, 0.005 mmol) and malice anhydride (1.0 g, 0.002 mmol) were placed in beaker (75 mL) and heated the mixture with constant stirring in oil bath at 170-180 ºC for 10 min until all the materials were fused to dark yellow liquid. Cool the solid for 5 min and recrystallized with ethanol (**Scheme-I**). The reaction process was followed regularly by TLC [21].

Synthesis of monomers (F2 and F3) (one pot reaction): In 150 mL beaker, compound **F1** (0.5 g, 0.0023 mmol), 20 mL of dimethyl sulfoxide (DMSO) and 0.034 mmol of $SOCl_2$ were mixed and heated on hot plate using magnetic stirrer at 20 ºC, and then added triethylamine (1.815 g, 0.0179 mmol) after 20 min. Finally, added sulfadiazine (0.575 g, 0.0023 mmol/chlorodizepoxide (0.688 g, 0.0023 mmol) into the mixture with constant stirring at 30 ºC for 30 min. The mixture was cooled on ice bath and leave until the precipitate was formed, filtered and dry the product (**Schemes II** and **III**) [22]. The reaction process was monitored by TLC.

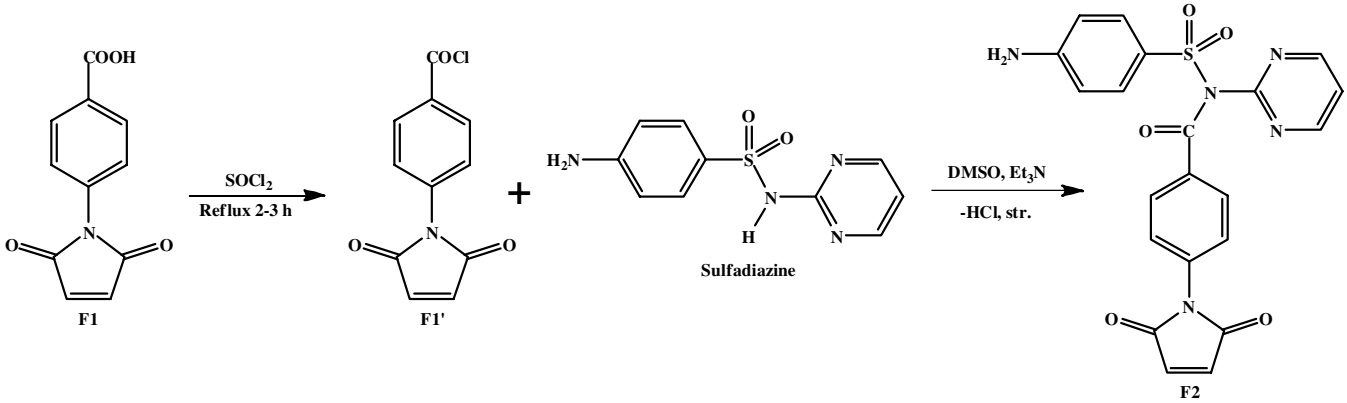


Scheme-I: Synthesis of compound **F1**

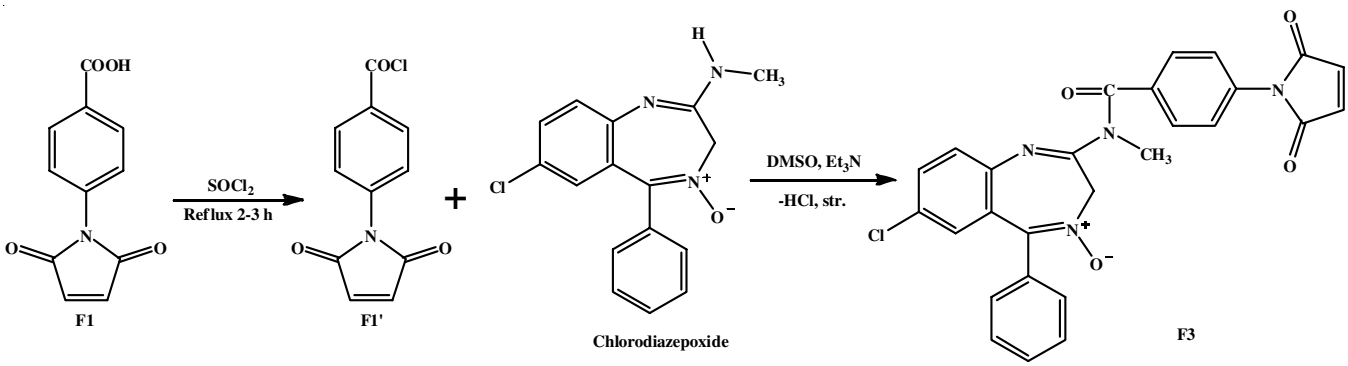
Synthesis of polymers: The polymerization process was done in both homogeneous and heterogeneous forms according to the literature [23].

Synthesis of homopolymers

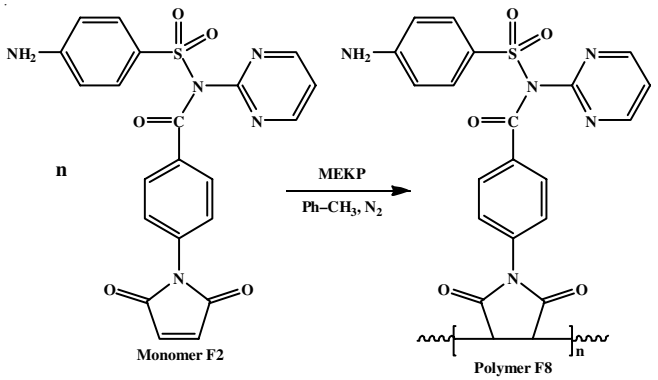
Synthesis of polymers (F8 and F9): Monomer (**F2/F3**) (0.02 g) was mixed with 10 mL of toluene in a 50 mL round bottom flask, which was tightly sealed and placed in a water bath at 90 ºC and added two drops of methyl ethyl ketone peroxide (MEKP), then pass the nitrogen gas from one of the flask nozzle. The reaction was continued for 2-3 h under reflux and at the end of polymerization, evaporate the solvent and filtered the precipitate and washed using diethyl ether and finally dried in an oven at 50 ºC (**Schemes IV** and **V**).



Scheme-II: Synthesis of monomer (**F2**)



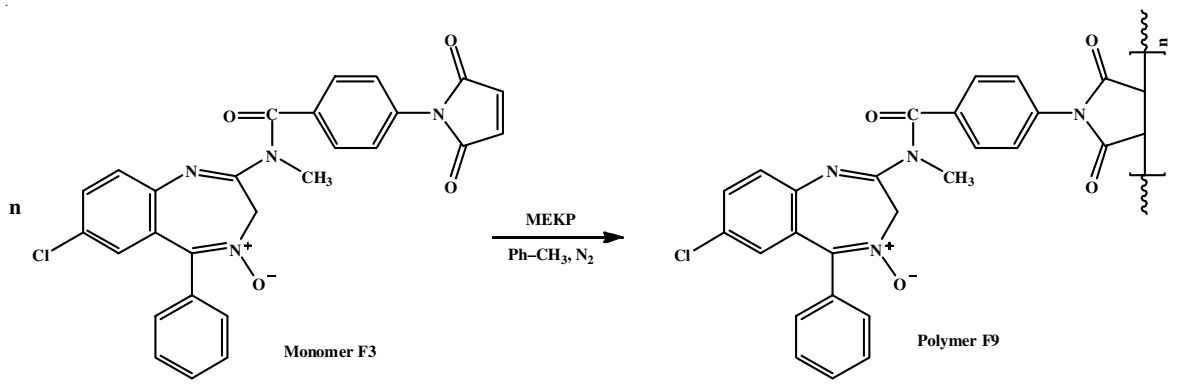
Scheme-III: Synthesis of monomer (**F3**)



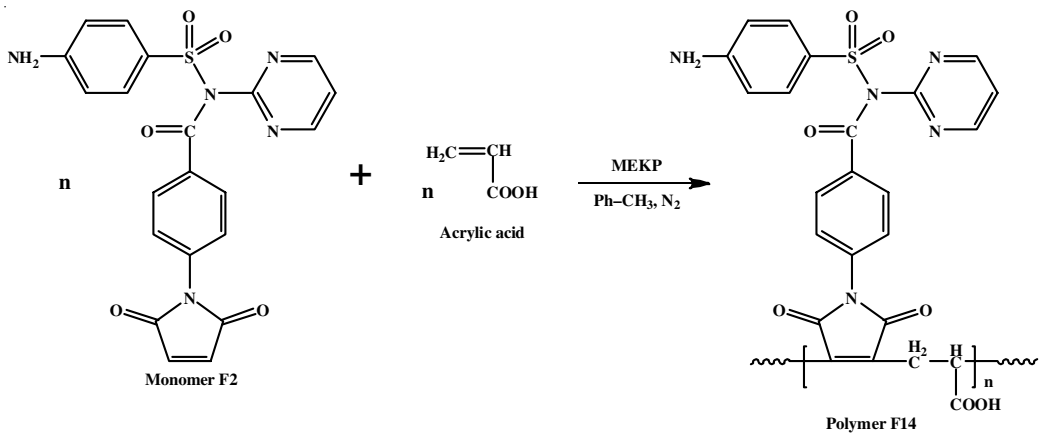
Scheme-IV: Synthesis of homopolymer (**F8**)

Synthesis of heteropolymers

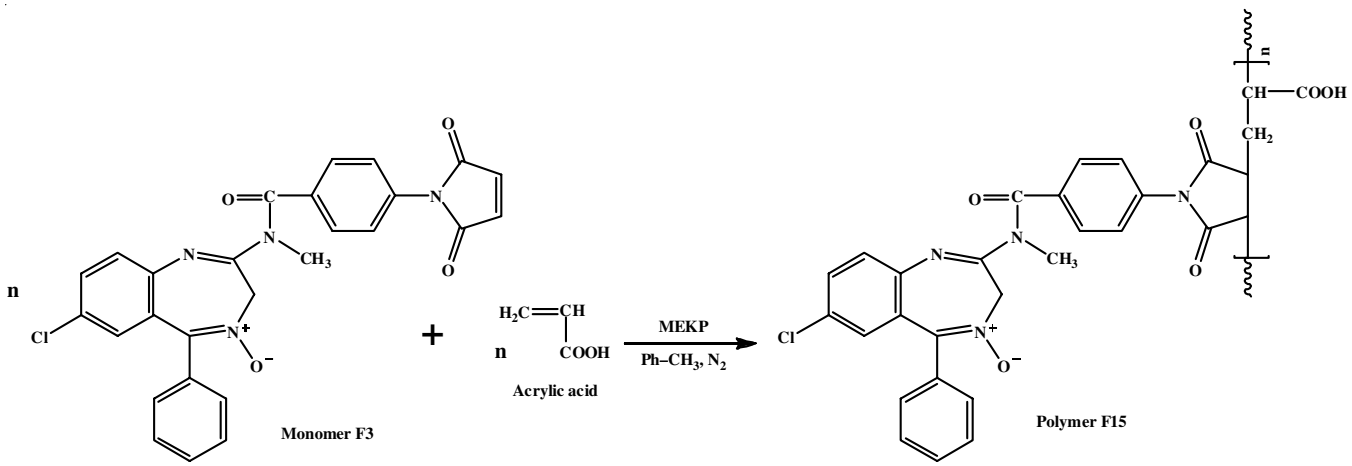
Synthesis of polymers (F14 and F15): In a tight sealed 50 mL roung bottom flask containing 0.2 g of monomer (**F2/F3**) in 10 mL of toluene and acrylic acid (0.033 g, 0.00045 mmol) was placed in a water bath at 90 °C and added two drops of methyl ethyl ketone peroxide (MEKP). The nitrogen gas was passed from one of the flask nozzle and the reaction continued for 2 h. At the end of polymerization, evaporate the solvent and filtered the precipitate and washed with diethyl ether and finally dried in an oven at 50 ºC (**Schemes VI** and **VII**). The physical properties of the both homo- and heteropolymers are given in Table-1.



Scheme-V: Synthesis of homopolymer (**F9**)



Scheme-VI: Synthesis of heteropolymer (**F14**)



Scheme-VII: Synthesis of heteropolymer (**F15**)

TABLE-1
PHYSICAL PROPERTIES OF PREPARED POLYMERS

Polymer	Colour	T (°C)	$t_{D,W}S$	$T_{unk}S$	d_{unk}	$d_{D.W}$	$\eta_{D.w}$ poise	η_{unk} poise
F8	Yellow	–	–	54	0.786	–	–	0.62
F9	Brown	–	–	58	0.782	–	0.904	0.67
F14	Light yellow	25	62	54	0.783	0.99	–	0.61
F15	Brown light	–	–	53	0.786	–	–	0.60

Swelling ratio: The swelling ratio was determined by immersing xerogel (0.05 g) from homo- and hetero polymers, in 50 mL of different buffer solutions (pH = 2.2, 7.0 and 8.0). It was allowed to soak for different period of time at constant temperature (310 K). After each 1 h and 24 h, hydrogel was removed from the water, blotted with filter paper to remove surface water weighed and then the swelling ratio was calculated using following equation [24]:

$$\text{Swelling ratio (\%)} = \frac{\text{wt. of hydrogel} - \text{wt. of xerogel}}{\text{wt. of hydrogel}} \times 100$$

Release of drugs: By using UV-visible spectrophotometer, the release of drug from the prepared polymers (both homo- and hetero polymers) was determined in three different buffer solutions (pH 2.2, 7.0 and 8.0) at constant temperature 310 K. By immersing xerogel (0.05 g) from homo- and hetero polymers in 50 mL of different buffer solutions, it was allowed to soak for different invertal of time at constant temperature 310 K. The hydrogel was removed from the buffer solution at the stipulated time and measure the absorbance of buffer solution in order to determine the amount of drug release [25].

RESULTS AND DISCUSSION

Characterization of compound F1: The appearance of characteristic absorption broad bands at 3500 ν(O-H), 3100 ν(C=C-H maleimide), 1705 ν(C=O carboxylic acid), 1602 ν(C=C benzoic acid). 1514 ν(C=C maleimide), 1380 ν(C-N-C), 1175 ν(C-O) 824 ν(*p*-substituted of benzene ring) and 697 ν(*o*-substituted of benzene ring) and 542 ν(C-C) [26]. ^{1}H NMR shows single-signal at δ 13 ppm for (OH) acid, and signal doublet at 8 ppm for (Ph-H), single-signal at 4 ppm for (C=C-H)maleimide and single-signal at 3.5 ppm for (N-C=C-H). ^{13}C NMR shows the signal at 166.60 ppm for (C=O) carboxylic acid and doublet signal at 130 ppm for (C=C)Ph, and single signal at 40 ppm for (C-O) carboxylic acid [27].

Characterization of monomers (F2 and F3): The FTIR spectra of monomer (**F2 and F3**) show the disappearance absorption band of O-H and appearance of absorption band of NH_2 at 3306 cm^{-1}, 3100 cm^{-1} C=C-H maleimide, 2997 cm^{-1} C=C-H benzamide (**F2**) and 2926 cm^{-1} (**F3**), 2923 cm^{-1} C=C-H ring of drug, 1710 cm^{-1} C=O amide, 1600 cm^{-1} (C-N-C), 1532 cm^{-1} C=C amide, 1381 cm^{-1} C-N, 1311 cm^{-1} C-N drug, 1256 cm^{-1} S=O, 1172 cm^{-1} C-O, 947 cm^{-1} C-S and 697 cm^{-1} S-N. The ^{1}H NMR shows the disappearance signal for (O-H) acid and appearance of a single signal at δ 11 ppm for (OH) drug, doublet signal at δ 8 ppm for (C=C-H)Ph, a single signal at δ 5 ppm for (C=C-H), δ 2 ppm for CH_3. The ^{13}C NMR also shows the disappearance signal at δ 170.67 ppm (C=O) acid and signal at δ 130 ppm for (C=C)Ph and at δ 40 ppm for (C-H_3).

The ^{1}H NMR spectrum for monomer (**F3**) shows disappearance a single signal at δ 13 ppm for (OH) acid and appearance signal at δ 8 ppm for (C=C-H)Ph, at δ 6 ppm for (C=C-H) maleimide and at δ 3 ppm for (C-H). The ^{13}C NMR spectrum for monomer (**F3**) showed the disappearance of signal for (C=O) acid and shows the signals at δ 130 ppm for (C=C)Ph and at δ 40 ppm for (C-C).

Characterization of homopolymers (F8 and F9): The FT-IR spectra of homopolymers (**F8** and **F9**) show the disappearance absorption band of C=C-H maleimide at 3100 and 3009 cm^{-1} respectively and the absorption bands at 2992 cm^{-1} C=C-H benzamide (**F8**) and C-C-H aliph at 2885 cm^{-1} (**F9**). The absorption band at 2885 cm^{-1} of C=C-H ring of drug (**F8**) is clearly visible. The absorption peaks of C=O amide at 1712 (**F8**) and 1711 cm^{-1} (**F9**), similarly C-N-C at 1693 (**F8**) and 1530 cm^{-1} (**F9**); at 1586 (C=C maleimide) (**F8**) and 1600 cm^{-1} (**F9**).

The ^{1}H NMR of polymer (**F8**) shows the single peak at δ 10 ppm for (O=C-H), multi-signals at δ 7-8 ppm for (C=C-H, H-Ar), at δ 3-4 ppm for (C-C-H)maleimide and at δ 1-3 ppm for (N-H). Similarly, ^{1}H NMR of polymer (**F9**) shows the multi-signals at δ 7-8 ppm for (C=C-H)Ph, at δ 3-4 ppm for (C-C-H)-maleimide and at δ 1-3 ppm for (C-H_3).

Characterization of heteropolymers (F14 and F15): The FT-IR spectra of heteropolymer (**F14**) show the disappearance absorption band of O-H and the appearance of absorption peaks at 3105 cm^{-1} C=C-H benzamide (**F14**). Similarly, heteropolymer (**F15**) shows the peak at 2929 cm^{-1} C-H aliph. The disappearance of absorption peak of C=C-H maleimide was found in both heteropolymers. Similarly, the absorption peaks at 3075 (**F14**) and 3010 cm^{-1} (**F15**) of C=CH acrylic acid, at 2981 cm^{-1} (**F14**) of C-C-H aliph, 1714 (**F14**) and 1711 cm^{-1} (**F15**) C=O amide; at 1602 cm^{-1} (**F14** and **F15**) C-N-C; at 1173 (**F14** and **F15**) C-O; at 1256 (**F14**) and 1381 cm^{-1} (**F15**) C-N were observed.

The ^{1}H NMR of polymer (**F14** and **F15**) shows the multi-signals at δ 7-8 ppm for (C=C-H)Ph, at δ 3-4 ppm for (C-C-H)maleimide, at δ 2-3 ppm for (C-OH)aliph and at δ 1 ppm for (C-H)aliph. For polymer **F15**, the single peak was observed at δ 10 ppm for (O=C-H).

Solubility: The solubility properties of prepared monomers and polymers in different solvents (H_2O, ethanol, $CHCl_3$, ether, toluene, DMSO, hexane, petroleum ether and acetone) were studied. The solubility results are shown in Table-2.

Swelling ratio: The swelling ratio was determined by immersing 0.05 g polymers in 50 mL of different buffer solutions (pH 2.2, 7.0 and 8.0) and allowed to soak for different period of time at 310 K. Table-3 represents the swelling ratio of homo and hetero polymers in different period of time.

Release of drug: By using UV-visible spectrophotometer, drug release from the prepared polymers (homo and hetero) was determined in three different buffer solutions (pH 2.2, 7.0 and 8.0) at 310 K. Table-4 represents the drug release from the prepared polymer.

TABLE-2
SOLUBILITY OF SYNTHESIZED MONOMERS AND POLYMERS

Monomer/ Polymer	H_2O	EtOH	$CHCl_3$	Ether	Toluene	DMSO	Hexane	Petroleum ether	Acetone
F1	+	Partial	+	–	Partial	+	Partial	–	+
F2	Partial	–	+	–	Partial	+	+	–	+
F3	Partial	–	+	–	Partial	+	+	–	+
F8	+	Partial	–	–	Partial	+	–	–	+
F9	+	+	–	–	Partial	+	–	–	+
F14	+	Partial	–	–	Partial	+	–	–	+
F15	+	+	–	–	Partial	+	–	–	+

TABLE-3
SWELLING RATIO (%) OF HOMO- AND HETERO-POLYMERS IN DIFFERENT pH AT 37 °C

Time	Types of polymers											
	Homo-polymer						Hetero-polymer					
	pH = 2.2		pH = 7.0		pH = 8.0		pH = 2.2		pH = 7.0		pH = 8.0	
	F8	**F9**	**F8**	**F9**	**F8**	**F9**	**F14**	**F15**	**F14**	**F15**	**F14**	**F15**
1 h	1.1857	0.1996	1.3806	0.3984	1.5600	0.5964	1.1857	0.1996	1.3806	0.3984	1.7681	1.1857
2 h	1.3806	0.3948	1.5740	0.5964	1.9607	0.8960	1.4980	0.3984	1.7681	0.5064	1.9607	1.3806
3 h	1.9600	0.4961	1.9607	0.7946	2.3437	1.0350	1.7681	0.4964	1.9607	0.7936	2.1526	1.7081
4 h	2.1526	0.7936	2.5341	0.8940	2.7237	1.3230	2.0240	0.6960	2.1526	0.9932	2.5341	1.9607
5 h	2.1526	0.7936	2.5341	0.8940	2.7237	1.3230	2.5341	0.8510	2.6341	1.5420	3.0000	2.2830
6 h	–	–	–	–	–	–	2.5341	1.0000	2.9126	1.5420	3.1007	2.3437
7 h	–	–	–	–	–	–	2.5341	1.0000	2.9126	1.5420	3.1007	2.3437
1 day	2.5341	1.1857	2.5356	1.3806	3.1090	1.5748	2.7237	1.7681	2.9126	1.9607	3.1007	2.1526
2 day	2.7237	1.3807	2.9126	1.5748	3.1960	1.7716	2.9126	1.9607	3.1007	2.1526	3.2882	2.3437
3 day	3.1007	1.5748	3.2882	1.7861	3.3420	1.8607	3.1007	2.1526	3.3608	2.2261	3.5261	2.5370
4 day	3.4749	1.7510	3.6608	1.9541	3.4520	2.0000	3.2882	2.3437	3.7461	2.4783	3.8950	2.7235
5 day	3.6608	1.9607	3.8650	2.1526	3.4630	2.1210	3.4749	2.5341	4.0307	2.4983	4.2145	3.0000
6 day	3.8461	2.0216	3.9112	2.3437	3.4670	2.2100	3.8461	2.7237	4.2145	2.5230	4.2145	3.2658
7 day	3.9943	2.1251	3.9313	2.5341	3.4740	2.4520	4.0307	2.7237	4.3417	2.5670	4.2145	3.4748
8 day	4.1263	2.1341	3.9313	2.7412	3.4740	2.4930	4.0307	2.7237	4.3417	2.5670	4.2145	3.4748
9 day	4.1263	2.1341	3.9313	2.7412	3.4740	2.4930	–	–	–	–	–	–

TABLE-4
RELEASE OF DRUG (λ) FOR HOMO- AND HETERO-POLYMERS IN DIFFERENT pH AT 310 K

Time	Types of polymers											
	Homo-polymer						Hetero-polymer					
	pH = 2.2		pH = 7.0		pH = 8.0		pH = 2.2		pH = 7.0		pH = 8.0	
	F8	**F9**	**F8**	**F9**	**F8**	**F9**	**F14**	**F15**	**F14**	**F15**	**F14**	**F15**
1 h	0.300	0.109	0.357	0.260	0.344	0.261	0.853	0.065	0.985	0.09	0.785	0.318
2 h	0.311	0.111	0.366	0.266	0.364	0.271	0.962	0.071	1.054	0.096	0.943	0.371
3 h	0.319	0.122	0.376	0.271	0.382	0.282	1.000	0.079	1.121	0.097	1.101	0.450
4 h	0.349	0.133	0.390	0.280	0.391	0.291	1.0321	0.087	1.209	0.099	1.256	0.496
5 h	0.349	0.133	0.390	0.280	0.391	0.291	1.121	0.093	1.308	0.121	1.350	0.595
6 h	–	–	–	–	–	–	1.223	0.100	1.404	0.121	1.534	0.671
7 h	–	–	–	–	–	–	1.223	0.100	1.404	0.121	1.534	0.671
1 day	1.235	0.150	2.213	0.144	1.356	0.310	1.220	0.121	2.000	0.138	3.000	0.556
2 day	1.563	0.160	2.517	0.148	1.541	0.352	1.349	0.125	2.311	0.140	3.247	0.675
3 day	2.032	0.170	2.697	0.159	1.981	0.368	1.367	0.132	2.529	0.151	3.534	0.775
4 day	2.308	0.209	3.000	0.194	2.540	0.397	1.496	0.153	2.787	0.176	3.747	0.854
5 day	2.606	0.243	3.187	0.228	3.150	0.530	1.852	0.159	3.079	0.205	4.000	0.938
6 day	2.921	0.322	3.699	0.276	3.681	0.590	2.116	0.165	3.328	0.234	4.000	0.985
7 day	2.999	0.421	4.000	0.367	4.000	0.621	2.421	0.165	3.622	0.234	4.000	1.000
8 day	3.460	0.442	4.000	0.474	4.000	0.834	2.421	0.165	3.622	0.234	4.000	1.000
9 day	3.460	0.442	4.000	0.474	4.000	0.834	–	–	–	–	–	–

Conclusion

In this work, the synthesis of compound (**F1**) is acheived *via* reaction of maleic anhydride with 4-aminobenzoic acid, which in turn was converted to acyl chloride derivative. Further acyl chloride derivative is reacted with amino drugs (sulfadiazine, chlordiazepoxide) to afford **F2** and **F3** monomers. A new polymers (homo and hetero) were prepared through the reaction of one based material and acrylic acid monomer to form target polymers. All the prepared monomers and polymers were characterized by FT-IR and ^{1}H-, ^{13}C NMR spectral analysis.

The controlled drug release and swelling % was performed in different pH values at 37 ºC. The swelling percentage value is varied in different polymers and this difference can be attributed due to the release of drug. It is also observed that process of releasing the drug in basic medium (pH 8) is greater than in acid medium (pH 2.2).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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