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Release Behavior of Biodegradable and Non-biodegradable Polymeric Microparticles Loaded with Nimesulide

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Abstract**—**This presentation narrates the comparative analysis of the dissolution data nimesulide microparticles prepared with ethylcellulose, hydroxypropyl methylcellulose, chitosan and Poly(D,L-lactide-co-glycolide) as polymers. The analysis of release profiles showed that the variations noted in the release behavior of nimesulide from various microparticulate formulations are due to the nature of used polymer. In addition, maximum retardation in the nimesulide release was observed with HPMC (floating particles). Thus HPMC miacroparticles may be preferably employed for sustained release dosage form development**.**

Keywords**—**Nimesulide, microparticles, ethylcellulose, hydroxypropyl methylcellulose, chitosan and Poly(D,L-lactide-co-glycolide).

I. Introduction

NIMESULIDE, abbreviated as EC, is a nonsteroidal anti-inflammatory drug. Sulfonanilide specie is present in its chemical structure which endow it acidic property. NIM acts as an excellent analgesic, antipyretic, and anti-inflammatory agent [1].Ethyl cellulose, abbreviated as EC, is widely employed for the encapsulation of active pharmaceutical ingredients due to its attractive properties e.g. non-toxic, non-irritating, biocompatible and non-biodegradable, for oral delivery of drugs. EC microparticles have also tendency to absorb high pressure which exhibits its capability to prevent fracture induction in its coating during tabletting [2].Hydroxypropyl methylcellulose, abbreviated as HPMC, is an excellent polymer that is widely used for the development of floating formulations to sustain the release of drugs for prolonged time [3].

Poly(D,L-lactide-co-glycolide), abbreviated as PLGA, is a biodegradable and biocompatible polymeric substance. It shows excellent characteristics as drug delivery devices for various drug molecules [4].Chitosan, abbreviated as CTN, is a natural biopolyaminosaccharine having the property of a weak base.

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Its solubility in dilute aqueous acidic solutions like 2% acetic acid solution has been determined due to the presence of free amino group.

This amino group helps in the formation of bonds between NIM and CTN which is responsible for its release controlling characteristic [5].

Our previous research articles [1-5] present the preparation and in-vitro characterization of nimesulide (NIM) microparticles using ethylcellulose (EC) [1,2], hydroxypropyl methylcellulose (HPMC) [3], chitosan (CTN) [4] and Poly(D,L-lactide-co-glycolide) (PLGA) [5] as polymers. This short review summarizes the comparison of dissolution behavior of NIM from the respective formulations as described below.

II. Experimental

NIM-EC microparticles were also prepared via non-solvent addition coacervation technique by dissolving a weighed amount of EC in toluene (50 mL) using magnetic stirrer followed by the addition of NIM. To induce coacervation by precipitating EC from solution, non-solvent liquid paraffin (100 mL) was gradually added. Microparticles were obtained by filtration, washed thrice with *n*-hexane (200 mL) and dried. Three different microparticulate formulations M1, M2 and M3 containing drug: polymer 1:1, 1:2 and 1:3 ratio, respectively were prepared [1].

NIM-EC microparticles were prepared via thermal change coacervation by dissolving a weighed amount of EC in cyclohexane (30 ml, heated at 70-80°C) stirred at 300-900 rpm using magnetic stirrer followed by the dispersion of NIM. To induce phase separation, polymer-drug mixture was cooled down resulting in the formation of microparticles. The microparticles were washed thrice with n-hexane (100 ml) and dried. Three different microparticulate formulations M1, M2 and M3 containing drug: polymer 1:1, 1:2 and 1:3 ratio, respectively were prepared [2].

NIM-HPMC microparticles were prepared via non-solvent addition coacervation by dissolving a weighed amount of HPMC in dichloromethane (20 ml) using magnetic stirrer followed by the addition of NIM. To induce coacervation, liquid paraffin (50 ml) was added gradually. Microparticles were obtained by filtration, washed thrice with *n*-hexane (200 mL) and dried. Three different microparticulate formulations M1, M2 and M3 containing drug: polymer 1:1, 1:2 and 1:3 ratio, respectively were prepared [3].

NIM-PLGA microparticles were developed via non-solvent addition coacervation by dissolving a weighed amount of PLGA in dichloromethane (12.5 ml) using magnetic stirrer followed by the addition of NIM. To induce coacervation, liquid paraffin (non-solvent, 12.5 ml) was added gradually. Microparticles were obtained by filtration and dried. Three different microparticulate formulations M1, M2 and M3 containing drug: polymer 1:1, 1:2 and 1:3 ratio, respectively were prepared [3].

NIM-CTN microparticles were fabricated via pH change coacervation by dissolving a weighed amount of CTN in 5 % v/v aqueous acetic acid using magnetic stirrer followed by the addition of NIM. To induce coacervation, polymer solution was added slowly into 2 M sodium hydroxide solution (350 ml) resulting in the formation of microparticles. Then, 3% w/v aqueous glutaraldehyde solution was added to harden the microparticles. Microparticles were obtained by filtration and dried. Three different microparticulate formulations M1, M2 and M3 containing drug: polymer 1:1, 1:2 and 1:3 ratio, respectively were prepared [3].

All the microparticulate formulations were analyzed physic-chemically. Dissolution testing was performed using USP dissolution apparatus II and water as dissolution medium (900 ml).

Then the dissolution data was analyzed using various model dependent and independent approaches like zero order, first order, Highuchi and Korsemeyer-Peppas models. The values of $t_{60\%}$ were also determined from zero order equation.

Results and discussion

It is noted from the results that the release of NIM from all microparticulate formulations is affected by the polymer quantity. Comparison between the dissolution data exhibited that 60% of NIM release was achieved in 2.73, ----, 7.2, 2.14 and 3.30 h from EC (Non-solvent addition coacervation), EC (Thermal change coacervation), HPMC, PLGA and CTN microparticles having 1:1 drug to polymer ratio. Comparison between the dissolution data exhibited that 60% of NIM release was achieved in 3.82, ----, 7.0, 5.0 and 3.38 h from EC (Non-solvent addition coacervation), EC (Thermal change coacervation), HPMC, PLGA and CTN microparticles having 1:2 drug to polymer ratio. Comparison between the dissolution data exhibited that 60% of NIM release was achieved in 6.25, ----, 12.2, 8.0 and 8.0 h from EC (Non-solvent addition coacervation), EC (Thermal change coacervation), HPMC, PLGA and CTN microparticles having 1:3 drug to polymer ratio. It is seen that there is a rapid release of NIM from all microparticles with 1:1 drug to polymer ratio and reverse behavior is observed with 1:3 drug to polymer ratio, which is confirmed by the $t_{60\%}$ values (Table 1). The reason for this rapid release could be due to the wall thinness of microparticles having 1:1 drug to polymer ratio which is not as efficient in retarding NIM dissolution as microparticles having 1:3 drug to polymer ratio. It can also be attributed to the quick formation of high number of pores in hydrated polymeric matrix resulting in the swift release of NIM when low quantity of polymer is used [1-4].

The release behavior of NIM from all formulations was biphasic which meant an early swift release followed by the sustained release of NIM. An early swift release is considered due to the release of NIM molecules attached at the surface of microparticles or in its periphery. The sustained release could be due to the release of NIM present in the core of the microparticles through the channels formed in the polymeric matrix. All the formulations with 1:1 drug to polymer showed a maximum early swift release which decreased with the increase in polymer concentration, ultimately least early swift release was seen with 1:3 drug to polymer. Based on early swift release, formulations can be ranked as follows: 1:1 > 1:2 > 1:3.

It is evident from results that Higuchi model was best fit to the dissolution data in the basis of highest linearity. Subsequently, the zero and first order models were best fit to the release profiles. Higuchi model elaborates diffusion controlled drug release. Diffusion controlled drug release from all these formulations is further ensured by the application of Korsmeyer-Peppas model to the dissolution data by calculating the value of release exponent (*n*). It is observed that anomalous mode (non-Fickian, a combination of the diffusion and erosion mechanism) of NIM release is followed by all microparticles except in case of NIM-PLGA that obeys case I transport i.e. same as zero order release.

TABLE I
RELEASE PROFILES OF DEVELOPED FORMULATIONS

Microparticles	Drug : Polymer	$t_{60\%}$ (h)	Best fit model	*n*
NIM-EC (Non-solvent addition coacervation)	1:1	2.73	Higuchi	0.52
	1:2	3.82	Higuchi	0.49
	1:3	6.25	Higuchi	0.49
NIM-EC (Thermal change coacervation)	1:1	2.27	Higuchi	0.42
	1:2	3.19	Higuchi	0.46
	1:3	5.98	Higuchi	0.49
NIM-HPMC	1:1	7.21	Higuchi	0.50
	1:2	10.10	Higuchi	0.50
	1:3	12.20	Higuchi	0.7
NIM-PLGA	1:1	2.14	Higuchi	>90
	1:2	3.38	Higuchi	>90
	1:3	8.01	Higuchi	>90
NIM-CTN	1:1	3.30	Higuchi	0.50
	1:2	5.00	Higuchi	0.50
	1:3	8.00	Higuchi	0.50

III. Conclusion

This comparative analysis of previous studies concludes that the variations noted in the release behavior of nimesulide from various microparticulate formulations are due to the nature of used polymer. In addition, maximum retardation in the nimesulide release was observed with HPMC (floating particles). Thus HPMC miacroparticles may be preferably employed for sustained release dosage form development.

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