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Guar gum based microcapsules for colonic delivery of albendazole: Development and *In-vitro* evaluation

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ABSTRACT

The present study was aimed to develop and evaluate Albendazole microcapsules using guar gum, a natural polymer for colon-specific delivery for better treatment of Helminthiasis, Filariasis, and colorectal cancer by avoiding the side effects. Microcapsules were prepared by the use of different concentrations of sodium alginate and guar gum. The polysaccharides guar gum reacted with sodium alginate in the presence of calcium chloride to form microcapsules with a polyelectrolyte complex membrane by electrostatic interactions between the two charged polymers. The microcapsules were then studied for entrapment efficiency, surface morphology and particle size analysis. *In vitro* drug release study in presence and absence of cecal content were also studied. Further, kinetic modellings were employed to find out release mechanisms. The entrapment efficiency was found to be in the range 20%-30%. Increase in concentration of sodium alginate and guar gum showed better platform for encapsulation because of low viscosity. Albendazole microcapsules were found almost spherical, free flowing and non-aggregated. The surfaces of microcapsules are porous and wavy. The particle size was in the range 600-1000µm and the particle size range is maximum for microcapsules with high concentration of sodium alginate and guar gum. The *in vitro* drug release of microcapsules in GI simulated conditions were done and found that the cumulative percentage release from all the drug loaded batches of microcapsules fall within the range of 53% to 99 % in 24 hours study and it was found that the %cumulative release in microcapsules encapsulated with guar gum was maximum for Batch F (93.85%) and minimum for Batch J (61.40%) in 24 hrs.. The results of in vitro release study indicated that the amount of drug release decreased significantly with an increase in guar gum concentration but it was reverse with respect to sodium alginate concentration. Also incorporation of guar gum as coating shows maximum release in anaerobic colonic condition with cecal content as well as lower release in GI simulated condition. The rate of drug release follows Korsmeyer- peppas model that is the drug release is by diffusion and erosion.

Keywords: Colon drug delivery, Albendazole, Guar gum, Sodium alginate, Microcapsule.

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INTRODUCTION

Oral route is considered to be most convenient for administration of drug to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorption from these regions of the gastrointestinal tract depends upon the physicochemical properties of the drug. Dosage forms that deliver drug into the colon rather than upper gastrointestinal tract offers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (Ulcerative colitis, Crohn's disease, carcinomas, and infections such as Helminthiasis and Amoebiasis) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drug in the upper gastrointestinal tract or unnecessary systemic absorption [1] The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of per orally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidases such special delivery system will have a fair chance to get their drug sufficiently absorbed after per oral application. The different approaches for targeting orally administered drugs to the colon include coating with pH-dependent polymers, design of timed-release dosage forms and utilization of carriers that are degraded exclusively by colonic bacteria [2,3].

Micro-encapsulation is now the most frequently employed method of producing controlled release dosage forms. Microcapsules developed for use in medicine consisting of solid or liquid core material containing one or more drugs enclosed in coating. For example in ionic cross-linking technique, dropping or spraying a sodium alginate solution into a calcium chloride or barium chloride solution produces microcapsules [4] The divalent calcium or barium ions crosslink the alginate formed gelled droplets. The polysaccharide guar gum reacted with sodium alginate in the presence of calcium chloride to form microcapsules with a polyelectrolyte complex membrane by electrostatic interactions between the two charged polymers [5] Natural polymers [6] as a controlling agent for delivering of drugs have received much interest in recent years. Biocompatibility and biodegradability of these materials provide good advantages for this reason. Natural polymers in fact could obviate toxicity or biodegradability problems (i.e. formation of localized granulomatous inflammation), possibility due to the use of synthetic materials. Guar gum is a natural non-ionic polysaccharide being used as drug carrier for colonic delivery system due to its release retarding property and susceptibility to microbial degradation. Guar gum is derived from the seeds of Cyamopsis tetragonolobus [7]. Guar gum is hydrophilic in nature and swells in cold water forming viscous colloidal dispersions or sols. This gelling property retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment [8,9]. Albendazole is a broad-spectrum anthelminthic agent used for the treatment of Neurocysticercosis,

Hydatid disease,Giardia infection and Filariasis[10] Albendazole is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility. This study selected Albendazole as a drug for formulating colonic drug delivery system to obtain better pharmacological effect because most of the worms reside in large intestinal part and to avoid side effects associated with albendazole therapy. In addition it was reported that albendazole can also be used to treat regional peritoneal carcinomatosis arising from colorectal origin [11].Thus the above observation prompted us to formulate and evaluate natural polymer based microcapsules of Albendazole, which targeted to colon for improving the pharmacological effect and avoiding the side effects. Different batches of Albendazole microcapsules were prepared using different concentration of polymers. The microcapsules were then studied for Entrapment efficiency, drug-polymer compatility, and surface morphology, *In vitro* drug release studies with and without cecal content and kinetic studies.

METHODS

Preparation of albendazole microcapsule with guar gum and sodium alginate polymers

The codes and contents of formulations prepared are shown in Table 1. The micro spheres were prepared by following and modifying the reported methods[12,13] by Mishra B *et al*. The principle is the polysaccharides guar gum reacted with sodium alginate in the presence of calcium chloride to form microcapsules with a polyelectrolyte complex membrane by electrostatic interactions between the two charged polysaccharides. Guar gum dispersions of 0.1, 0.2 and 0.4%w/v were prepared by dispersing guar gum 0.1g, 0.2g, 0.4g respectively 100ml distilled water with continuous stirring using a magnetic stirrer followed by dissolving calcium chloride (1.5g). The pH of the solution was adjusted to 5.5 with 10% sodium hydroxide solution and this solution was used in the encapsulating procedure. Alginate solutions of 1.5, 2.0 and 2.5%w/v were then prepared by dissolving sodium alginate 1.5g, 2g and 2.5g in distilled water (100ml). Albendazole (0.4g) was dispersed in to 20ml of this solution using a magnetic stirrer. The sodium alginate solution containing Albendazole was loaded into a syringe fitted with 23G needle.100ml of guar gum-calcium chloride solution was taken in a beaker. Alginate-Albendazole solution was added drop wise at constant rate of 30ml/hr to guar gum-calcium chloride solution with constant stirring (100rpm).Reaction time of one hour was used. After forming microcapsules it was filtered and washed three times with distilled waster. The microcapsules were then hardened with acetone and dried by keeping it in a vaccum desicator.

Morphological evaluation of microcapsules

Shape and surface characteristics of Microcapsules were studied using Scanning Electron Microscope (SEM Philips 200 FEI). Sizes of Mc were evaluated using optical microscope. Since Mc was irregular after drying the longest diameter was measured. Fifty Microcapsules per formulation were evaluated. Average diameter was then calculated.

Drug loading

25mg of microcapsule were crushed in to powder and treated with 47.5ml 0.1N hydrochloric acid+ 2.5ml methanol. The resulting mixture was stirred at 250rpm. The temperature was maintained at 37±0.2^{0}C. At the end of 2 hrs, it was filtered, filtrate was analyzed spectrophotometrically at 309nm (Shimadzu UV 1700, Japan).

In vitro drug release study under simulated GI conditions

In vitro drug release characteristics of Mc were evaluated following reported method (Mishra *et al*[12] 2003) with little modification. 50mg of the prepared microcapsules were placed in a 100ml beaker and contacted with 50ml elution medium with maintained temperature (37+_0.2^{0}C) and stirring(50rpm) with small Teflon coated magnetic bead, by placing the beaker on energy regulated temperature controlled hot plate magnetic stirrer. The dissolution was conducted in dissolution medium of pH1.2 for the first two hours followed by dissolution medium of pH 6.8 up to 24 hrs. The dissolution medium of pH 1.2 was prepared by first making 100ml solution containing 2.5ml methanolic HCl and 97.5ml 0.1N HCl, 5ml of this solution make upto 50ml with 0.1N HCl, The dissolution medium of pH 6.8 was prepared by taking 49ml of the above medium and 51ml of 0.1 N NaOH. Samples were withdrawn every half an hour for 2 hrs in the case of dissolution medium of pH 1.2. After two hours the medium was replaced with dissolution medium of pH 6.8 and samples were withdrawn at one hour interval up to 6 hrs and then samples were withdrawn at 8th, 12thand 24th hour.5ml of the samples were withdrawn and replaced with 5ml of the dissolution medium. The samples were analyzed spectrophotometrically at 309 nm with suitable dilution.

In vitro release study under GI simulated conditions in presence of cecal content

To access the susceptibility of guar gum being acted upon by the colonic bacteria drug release studies were carried out in the presence of rat's cecal contents, because of the similarity with the human intestinal micro flora. The cecal content was collected from rat. As the cecum is naturally anaerobic, all those operations were carried out under anaerobic conditions. The drug release studies were carried out in a closed sterile beaker. The anaerobic condition is maintained by bubbling CO_2 into the dissolution medium.50 mg of the prepared microcapsules were placed in a 100ml beaker and contacted with 50ml elution medium and maintained temperature (37+- 0.2^{0}C) and stirring at 50rpm with a small Teflon coated magnetic bead, by placing the beaker on energy regulated temperature controlled hot plate magnetic stirrer. The dissolution was conducted in dissolution medium of pH 1.2 for the first two hours followed by dissolution medium of pH 6.8 upto 24 hrs. At the end 5th hour cecal content was transferred into the dissolution medium and maintain the anaerobic condition. Samples were withdrawn every half an hour for 2 hrs and one hour interval upto 5 hrs. After transferring the cecal content the samples were withdrawn at 6th, 8th, 12th and 24th hour. 5ml of the samples were withdrawn and replaced with 5ml of the freshly prepared dissolution medium. The samples were analyzed spectrophotometrically at 309nm with suitable dilution.

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Mathematical modeling of albendazole microcapsules

In order to investigate the mode of release from the microcapsules, the release data were analyzed with the following mathematical models.

$Q_t = K_0 t$ (Zero Order Kinetics)
$\text{Log}(Q_t / Q_0) = -K_1 t / 2.303$ (First order Kinetics)
$Q_t = K_{KP} t^n$ (Korsmeyer and Peppas equation)
$Q_t = K_H t^{1/2}$ (Higuchi's equation)

Where, Q_t is the percent of drug released at time't', K_0, K_1, K_{HC}, K_{KP} and K_H are the coefficients of Zero order, First order, Korsmeyer-Peppas and Higuchi's equations.

RESULTS AND DISCUSSION

The entrapment efficiency of all the formulations was determined and the results are shown in Table no: 2. the entrapment efficiency was in the range 20%-30%. Increase in concentration of sodium alginate and guar gum showed better platform for encapsulation because of low viscosity. The particle size analyses of formulations were carried out by using optical microscopy. For determining the particle size 50 microcapsules were selected randomly and the size was determined and fitted with standard micrometer scale. The results shown in Fig no:1.The particle size was in the range 600-1000µm and the maximum particle size range was found 700-750 µm in Albendazole microcapsules with sodium alginate and guar gum for Batch J. So it can be concluded that the particle size range is maximum for microcapsules with high concentration of sodium alginate and guar gum. The surface morphology of Albendazole microcapsules was seen by Scanning Electron Microscope. The ability to resolve various shapes helps the investigator determine whether a sample is morphologically homogenous and the presence of other materials can be detected. The surface morphology was done for Batch H with magnifications 30x, 100x, 500x and 1500x and shown in Fig no: 2 & 3.Albendazole microcapsules were found almost spherical, free flowing and non-aggregated. The surface of microcapsules are porous and wavy.The *in vitro* drug release of microcapsules in GI simulated conditions were done and it is seen from the observation data that the cumulative percentage release from all the drug loaded batches of microcapsules fall within the range of 53 % to 99 % in 24 hours study and it was found that the %cumulative release in microcapsules encapsulated with guar gum was found to be maximum for Batch F (93.85%) and minimum for Batch J (61.40%) in 24 hrs.The results of in vitro release study indicated that the amount of drug release decreased significantly with an increase in guar gum concentration[14] but it was reverse with respect to sodium alginate concentration and is attributed to increase in the diffusional path length, which the drug molecule have to traverse. It was found that the release of drug from all drug loaded batches was found to follow a biphasic pattern, that was an initial burst release of 34 % to 65 % during the second hour and the remaining amount of drug was found to be released in a slow or sustained manner for a period of 24 hours. As the polymers guar gum were mainly degraded by the colonic bacteria, simulated *in vitro* release in presence of rat cecal

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content were conducted .From the results it was found that the *in* vitro drug release of Batch J (2.5% of sodium alginate and 0.4% guar gum) was 61.40% without cecal content at the end of 24 hr where as with cecal content it was 98.92% (Fig no: 5).So, incorporation of guar gum as coating shows maximum release in anaerobic colonic condition with cecal content as well as lower release in GI simulated condition.

Various kinetic data studies were done including zero order, first order, Higuchi model, Korsmeyer-peppas model and Hixson-Crowell model and the results are shown in Fig no:6-9.The results shown that almost all formulations follows Korsmeyer- peppas model that is the drug release is by diffusion and erosion in GI simulated conditions but showed burst release in colonic conditions.

CONCLUSION

The results of in vitro release study indicated that the amount of drug release decreased significantly with an increase in guar gum concentration but it was reverse with respect to sodium alginate concentration. Also incorporation of guar gum as coating shows maximum release in anaerobic colonic condition with cecal content as well as lower release in GI simulated condition. The rate of drug release follows Korsmeyer- peppas model that is the drug release is by diffusion and erosion

Table No: 1: **Ingredients used for each formulations**

S.NO	INGREDIENTS USED IN(mg)	FORMULATIONS				
		F	G	H	I	J
1	Albendazole	400	400	400	400	400
2	Sodium alginate	1.5	2	2.5	2.5	2.5
4.	Guar gum	400	400	100	200	400
6	Calcium chloride	1500	1500	1500	1500	1500

Table No: 2: Entrapment efficiency of Albendazole microcapsules

S.NO	Formulations	Entrapment efficiency (%)
1	F	23.67
2	G	26.64
3	H	20.99
4	I	27.51
5	J	28.09

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Fig No: 1: Particle size analysis

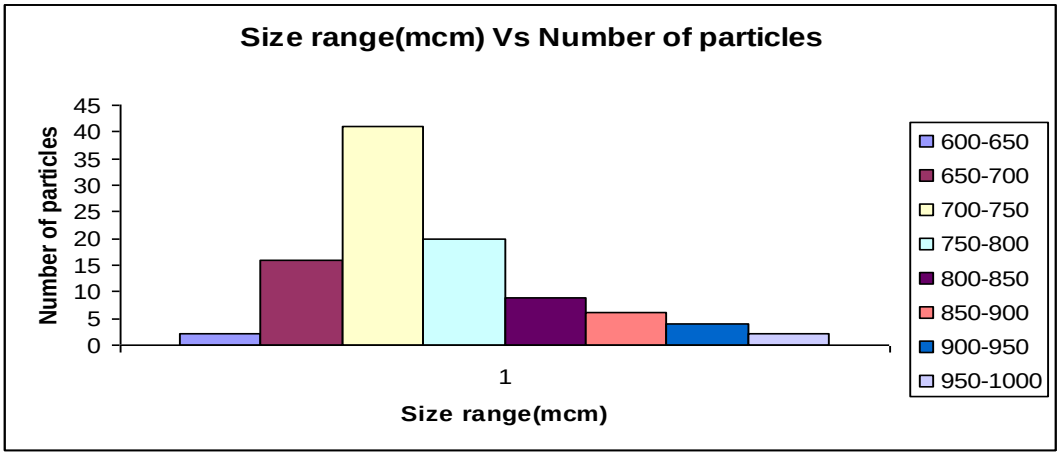

Fig No: 2: SEM of Batch- H (30x, 500µm)

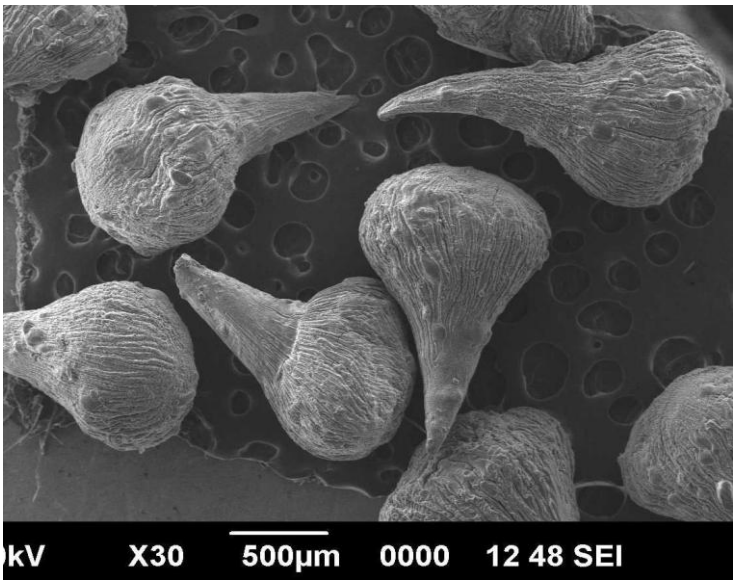

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Fig No: 3: SEM of Batch- H (1500x, 10µm

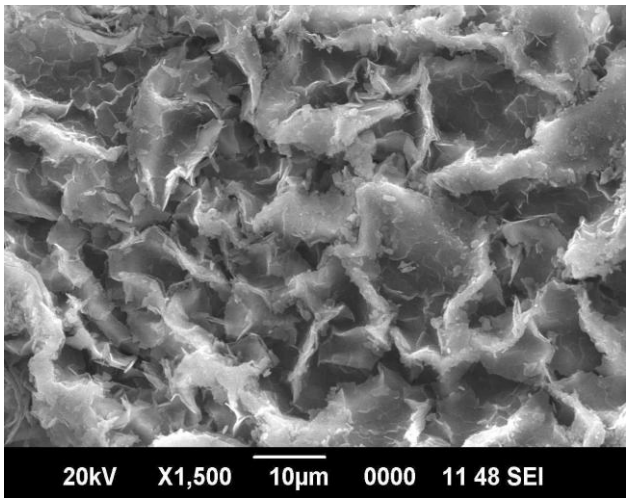

Fig no: 4: *In vitro* release of Albendazole from Batch- J microcapsules under GI simulated condition.

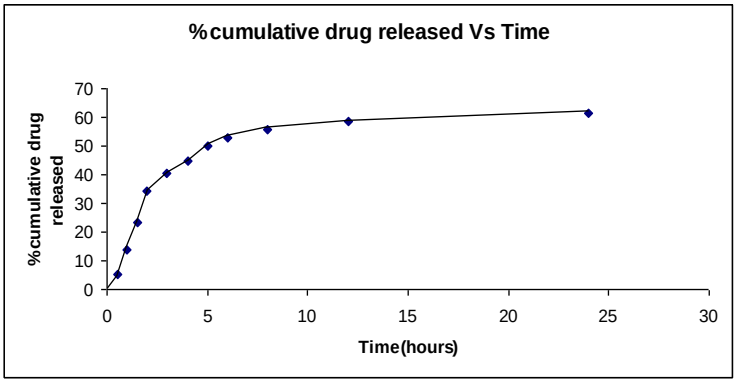

Fig no: 5: *In vitro* release of Albendazole from Batch- J microcapsules with and without cecal content.

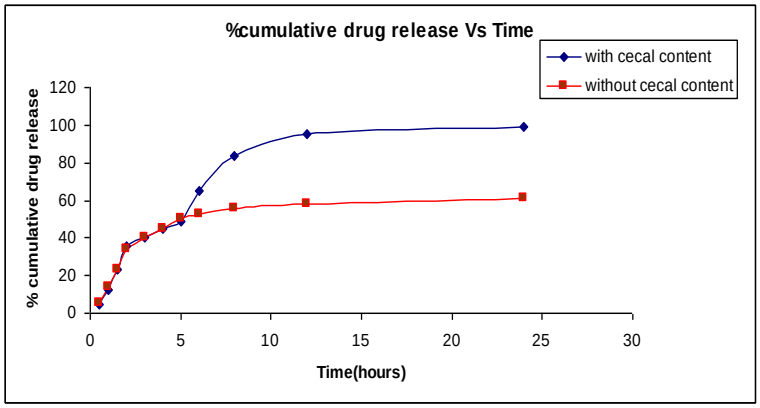

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Fig no: 6: Zero order release rate of Batch-J

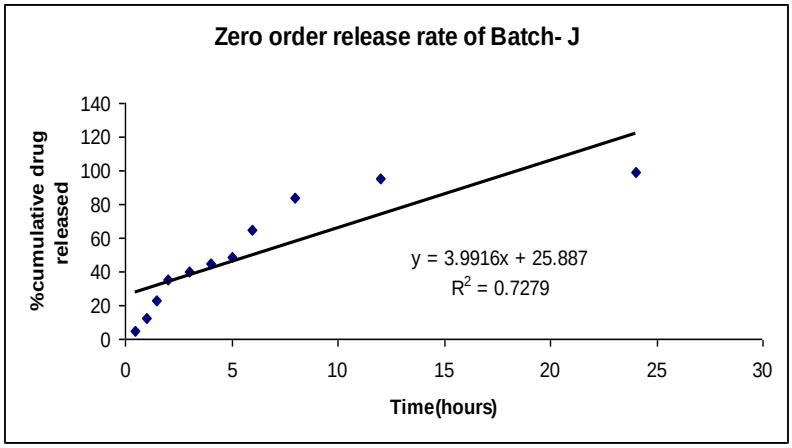

Fig no: 7: First order release rate of Batch-J

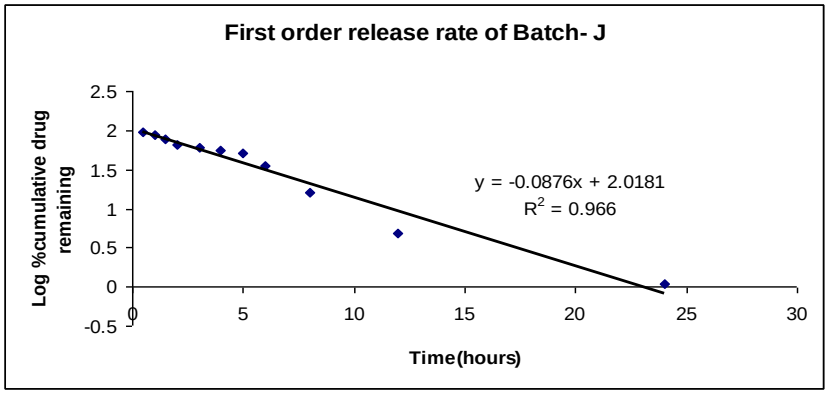

Fig no: 8: Higuchi plot of Batch J

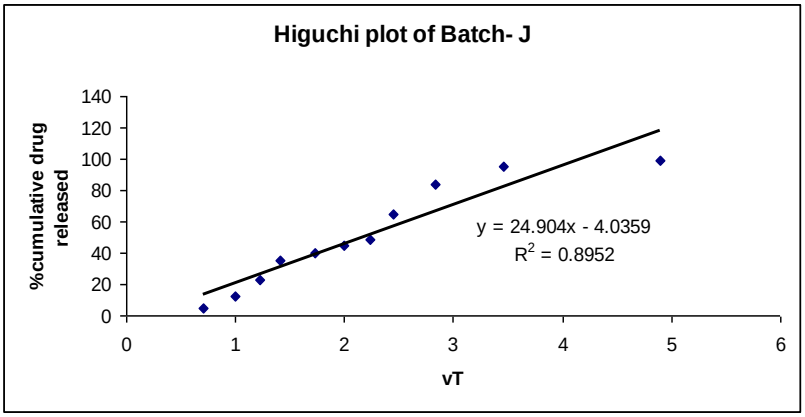

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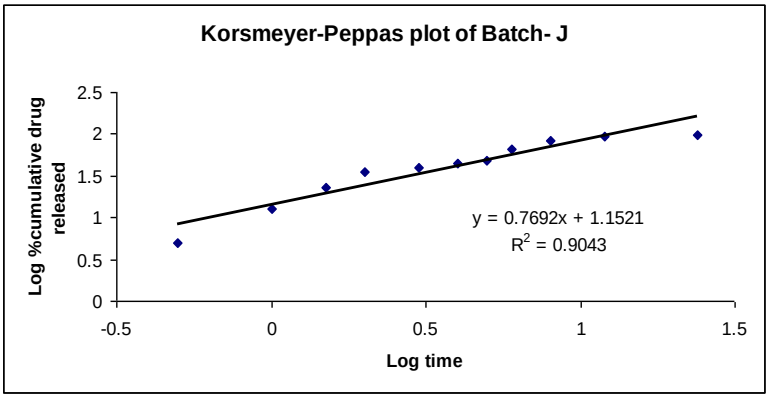
Fig no: 9: Korsmeyer-peppas plot of Batch-J



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