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FORMULATION AND EVALUATION OF GLIMEPIRIDE (SULFONYLUREA DERIVATIVE) MICROSPHERES BY NATURAL POLYMER

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Background: Microspheres are the carrier linked drug delivery system in which particle size is ranges from 1-1000 µm range in diameter having a core of drug and entirely outer layers of polymer as coating material. The present study aimed at developing a microsphere of glimepiride using natural polymer for a longer duration of action.

Material and methods: We formulated and evaluated of microspheres by natural polymer of Glimepiride and their Benefits of microsphere in drug delivery system. Microspheres of glimepiride was formulated using natural polymer chitosan. Antidiabetic effect of glimepiride microspheres and

Results: Particle size of each microsphere was found to have controlled average diameter ranging from 70 to 100 µm with micromeritic characters comprising bulk density between 0.292±0.19 and 0.388±0.09 gm/cc and tapped density from 0.329±0.19 to 0.458±0.09 gm/cc, Hausner's ratio

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between 1.070±0.04 and 1.224±0.03, angle of repose between 12.76±0.55 º and 24.71±0.44 º indicating that microspheres were within the pharmacopeia specification.

Percentage yield was between 69.49± 0.64 % to 89.97±0.66%, Swelling index of 0.5 to 0.7, 75 to 90 % mucoadhesion and a satisfactory level of drug entrapment capacity within 50 to 80 % range; all of which indicated a result of varying degree of individual performance due to optimum polymeric interaction, surface morphology showing SEM images and zeta potential between - 45.15 ± 0.97 mv found in batch AM whereas maximum charge of +54.09±0.73mv found in batch M6 proving acceptability relating to selection of optimized formula.

Conclusion: Microspheres of glimepiride was successfully developed using natural polymer chitosan.

Introduction:

The FDA approved glimepiride, a second-generation sulfonylurea, in 1995 with the goal of helping persons with type 2 diabetes mellitus improve their glycemic control.[1] In individuals without atherosclerotic cardiovascular disease and haemoglobin A1c levels below goal, it can be used as a second-line medication in combination therapy with metformin to treat type 2 diabetes mellitus.[2] It's also important to remember that the FDA has only authorised glimepiride as a sulfonylurea for use in combination therapy with insulin in individuals who do not respond well to combination therapy.(Source) For individuals who cannot take metformin, glimepiride is also used as a monotherapy.[3]

Because of its improved safety, glimepiride is occasionally referred to as a third-generation sulfonylurea. Furthermore, unlike other sulfonylureas, glimepiride does not affect the ischemic preconditioning of cardiac myocytes, defined as an adaptive physiological mechanism in response to an ischemic event to delay infarction and limit cardiac tissue damage. Researchers postulate that glimepiride selectively blocks sarcolemmal ATP-dependent potassium channels in cardiac myocytes over mitochondrial potassium channels, maintaining myocardial preconditioning [6]. This difference from other drugs in the class means that the use of glimepiride may be safer and more ideal in patients with cardiovascular comorbidities.

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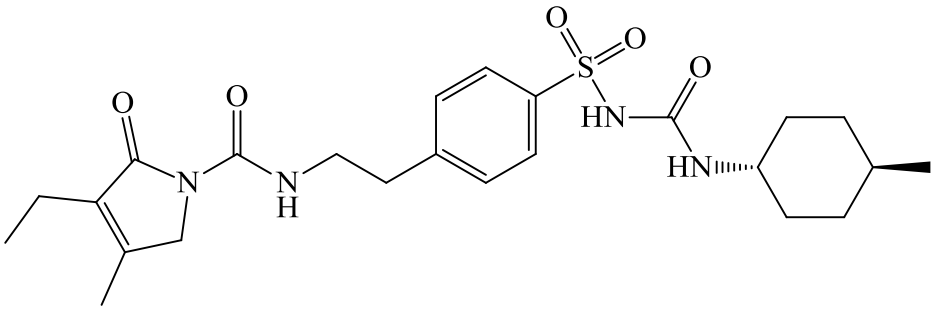

Glimepiride

Targeted Drug delivery system

Designated drug conveyance is a high-level strategy for conveying medications to the patients in such a designated succession that expands the centralization of conveyed medication to the designated body part of revenue just (organs/tissues/cells) which thusly improves viability of treatment by diminishing results of medication organization [Vyas and Khar, 2008]. Designated drug conveyance framework is liked over ordinary medication conveyance frameworks because of three principle reasons. The first being drug reason customary medications have low solvency and more medication flimsiness in contrast with designated drug conveyance frameworks. Furthermore, ordinary medications additionally have poor ingestion, more limited half-life and require huge volume of circulation. These comprise its pharmacokinetic properties. The third explanation establishes the Pharmacodynamic properties of medications.

Targeted drug delivery is a sort of shrewd medication conveyance framework which is supernatural in conveying the medication to a patient. [Allen and Cullis, 2004]. Transporter is one of the exceptional atoms or frame work basically needed for successful transportation of stacked medication up to the pre-chosen locales [Gujral and Khatri, 2013].

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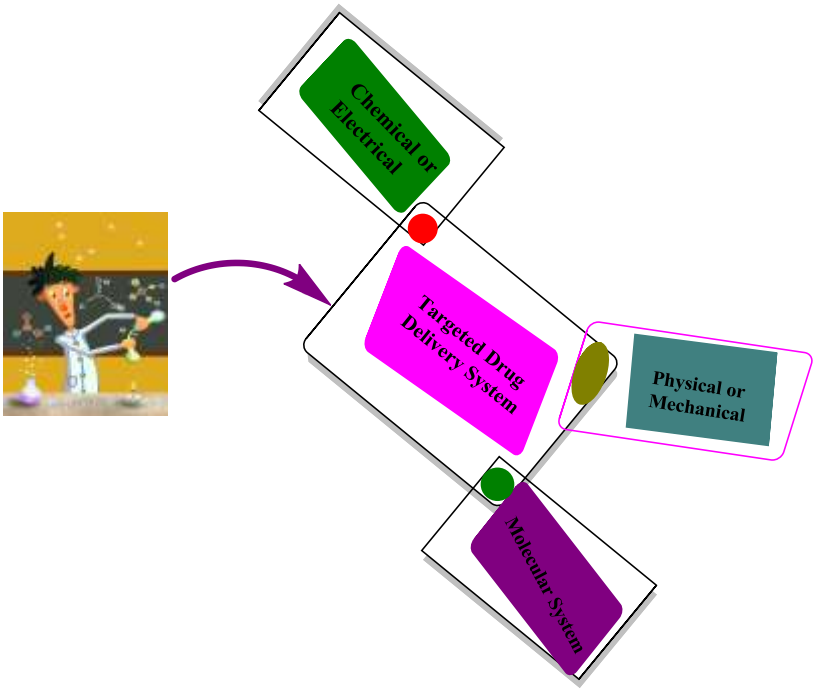

Fig.1 Targeted Drug delivery system**.**

Natural polymers for targeted drug delivery system

The utilization of regular polymers and polymethacrylates as medication transporters is one of the principle goals of analysts managing long-acting measurements structures [Tiwari and Shukla, 2009]. They are exceptionally steady, protected, non-poisonous, and hydrophilic and gel shaping in nature. In the course of recent years, the utilization of regular polymers in the plan of medication conveyance definition has gotten a lot of consideration because of their phenomenal biocompatibility and biodegradability.

Xanthan gum:

Xanthan gum is a high sub-atomic weight extra cell polysaccharide created by the aging of the gram-negative bacterium Xanthomonas campestris. In one of the preliminaries, xanthan gum showed a higher capacity to hinder the medication discharge than engineered hydroxy proyl-methyl cellulose [Bhardwaj et al., 2000].

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Chitosan:

Chitin after alkaline deacetylation is added in acid, filtered and the precipitate formed is washed and dried to get amine free chitosan. Synthetically, it's anything but a poly (N-glucosamine). Chitosan has good natural properties like nontoxicity, biocompatibility and biodegradability. A pH-touchy medication conveyance transporter has likewise been accounted for chitosan-based hydrogels [Tozaki et al., 2002]. Chitosan is a powerless base and is insoluble in water and natural solvents, in any case, it is dissolvable in weaken fluid acidic arrangement (pH < 6.5), which can change over the glucosamine units into a dissolvable structure R–NH3+. [Chandy and Sharma, 1990].

Microspheres as drug delivery carrier

Microspheres can be produced from different normal and engineered materials. Glass microspheres, polymer microspheres and artistic microspheres are monetarily accessible. Similarly, in pharmaceutical field different types of microspheres such as magnetic microsphere floating microsphere, polymeric microsphere, bio adhesive microsphere, biodegradable microsphere etc. are extensively tried for different controlled release dosage forms [Moy et al., 2011].

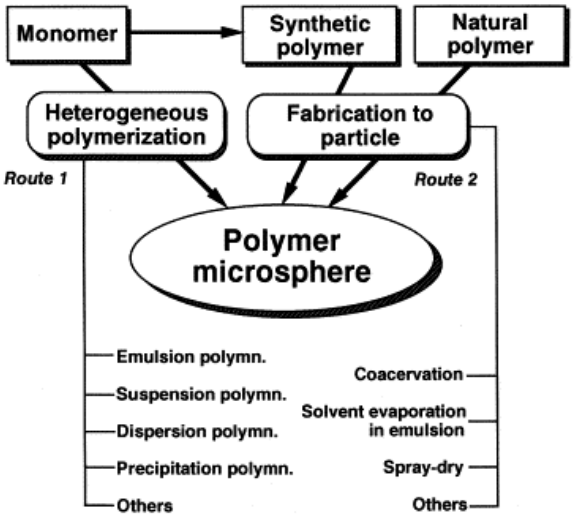

Fig 2: Functional polymer microspheres.

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Method of preparation of microspheres

There exist several methods to prepare microsphere that differ as per the characteristics of polymers used, nature of microspheres, and nature of manufacturing condition. These are described as following:

Spray Drying:

In Spray Drying the polymer is first broken down in an appropriate unpredictable natural dissolvable like dichloromethane, Acetone, and so on the medication in the strong structure is then scattered in the polymer arrangement under fast homogenization. This scattering is then atomized in a flood of hot air. [Mathew Sam et al., 2008 & Ghulam et al.,2009].

Solvent Evaporation:

The method is completed in a liquid assembling vehicle. A centre material to be microencapsulated is disintegrated or scattered in the covering polymer arrangement. With disturbance the centre material combination is scattered in the fluid assembling vehicle stage to acquire the fitting size microcapsule. [Trivedi et al., 2008 & Kannan et al., 2009].

Single emulsion technique:

The micro particulate transporters of normal polymers of regular polymers i.e., those of proteins and carbs are set up by single emulsion procedure. Regular polymers are broken down or scattered in fluid medium followed by scattering in non-watery medium like oil. Next cross connecting of the scattered globule is completed. [Pradesh et al., 2005].

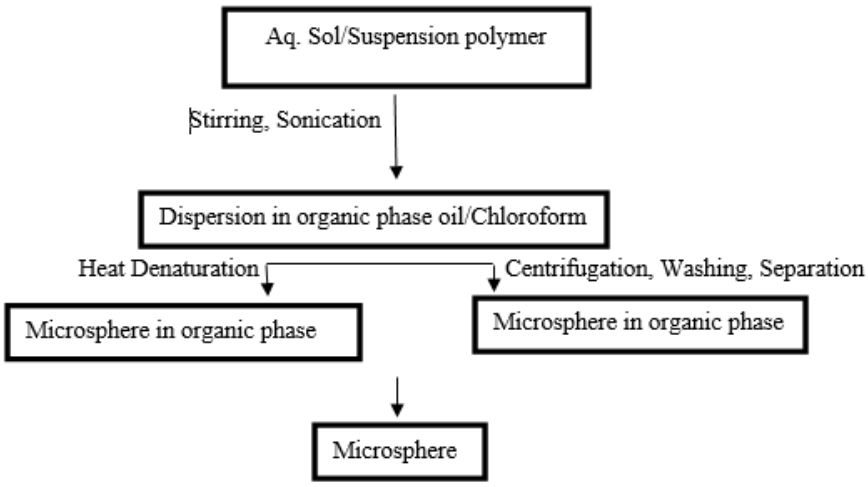

Fig 3: Single emulsion technique.

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Standard Curve of Glimepiride with 0.1N HCI :

100 mg of Glimepiride was precisely weighed and disintegrated in a little bit of methanol and made the volume with 0.1N HCl then the volume made up to 100 ml with 0.1N HCl. This was the primary stock solution, contained centralization of 1000g/ml. From this solution 10ml was precisely pipetted out and moved in to a 100 ml volumetric cup and volume was made up to 100ml with 0.1N HCl which contained the grouping of 100g/ml. From the second stock arrangement again 10ml was pipette out and weakened upto100ml with 0.1N HCl to get grouping of 10g/ml.

Preparation of Phosphate Buffer P^H 6.833:

Placed 11.45 gm of potassium dihydrogen phosphate & 28.80gms of disodium hydrogen phosphate and make upto1000mlwithdistilled water.

Standard Curve of Glimepiride with Phosphate Buffer P^H 6.8:

100 mg of Glimepiride was precisely measured and disintegrated in a little bit of methanol and make the volume with phosphate buffer pH 6.8 in a 100ml volumetric jar. This was the primary stock solution, consist concentration of1000g/ml. From this primary stock solution 10m1 was precisely pipetted out and moved in to a 100ml volumetric flagon and volume was made up to 100ml with primary stock solution pH 6.8 which contained the convergence of 100g/ml.

PREPARATION OF CHITOSAN MICRO SPHERE OF GLIMEPIRIDE SODIUM[13]:

Micro spheres are matrix system that contains drug all through their design and are possible possibility for oral controlled release. Microsphere can be characterized as solid circular particles going from one to 1000µm in size. These particles comprise of the medication which is the center material, and a covering material. Chitosan microspheres were set up by ionotropic gelation strategy.

Table: FORMULATIONS OF GLIMEPIRIDE CHITOSAN MICROSPHERES

S.No	Formulation Code	Glimepiride (gm)	Chitosan(gm)	Sod. TPP (gm)
1	F_1	0.1	0.9	0.2
2	F_2	0.1	0.8	0.2
3	F_3	0.1	0.7	0.2
4	F_4	0.1	0.6	0.2

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5	F_5	0.1	0.5	0.2
6	F_6	0.1	0.4	0.2
7	F_7	0.1	0.3	0.2
8	F8	0.1	0.2	0.2

EVALUATION OF MICROSPHERES

Particle size analysis :

Molecule size examination assumes a significant part in deciding their rent qualities and chitosan property. Mean molecule size for all definition was dictated by isolating the complete weight size of plan to % all out weight of chitosan.

Drug Entrapment :

Powdered microspheres were broken up with 10ml ethanol in 100ml volumetric jar and made the volume with 0.1N HCl. This subsequent liquid was than filtered by Whatsman filter paper No.44. After filtration, from this solution 10ml was taken out and weakened up to 100ml with 0.1NHCl. The rate drug capture was determined as follows.

$$\text{Drug entrapment} = \frac{\text{Determined medication fixation}}{\text{Theoretical drug concentration}} \% \times 100$$

Determination of True Density :

The true density of chitosan micro spheres was dictated by liquid displacement method. Apycno meter was utilized to decide find true density. The pycnometer was discharged and measured chitosan microspheres was added not weight was noted.

$$\text{Density of liquid (p)} = \frac{b \square a}{25}$$

$$\text{True density} = \frac{c \square a}{25 \square \square d \square c \square}$$

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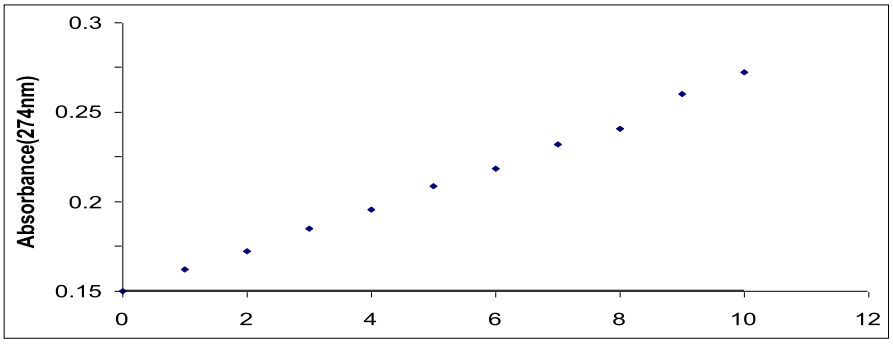
RESULT AND DISCUSSION

Table: Show S standard Curve In0.1n HCL

S.NO	Concentration (g/ml)	Absorbance(275nm)
1.	0	0
2.	1	0.024
3.	2	0.045
4.	3	0.07
5.	4	0.091
6.	5	0.117
7.	6	0.137
8.	7	0.164
9.	8	0.182
10.	9	0.22
11.	10	0.245

r^2= 0.9981 Y=0.0243

GRAPH: STANDARD CURVE IN0.1NHCl



Concentration (g/ml)

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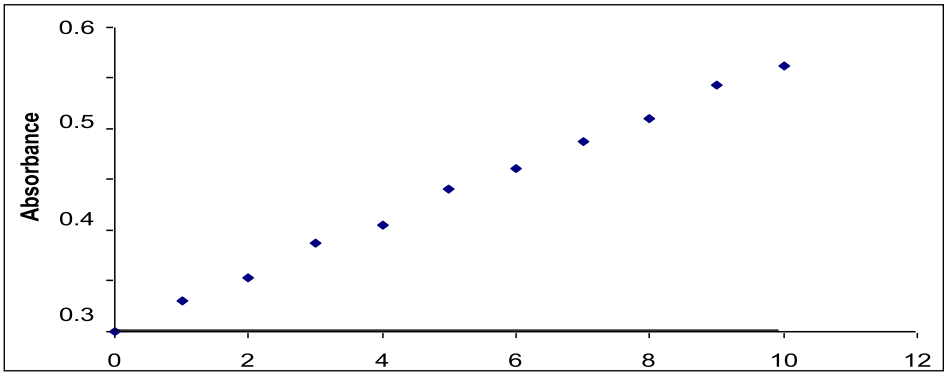
Table : INDICATES STANDARD CURVE IN PHOSPHATE BUFFER pH6.8

S.No	Concentration (□g/ml)	Absorbance(275nm)
1.	0	0
2.	1	0.060
3.	2	0.107
4.	3	0.175
5.	4	0.210
6.	5	0.281
7.	6	0.322
8.	7	0.375
9.	8	0.421
10.	9	0.458
11.	10	0.523

r^2=0.9990 Y=0.0519

GRAPH 2: STANDARD CURVE INPHASPHATE BUFFER pH 6.8



Concentration (g/ml)

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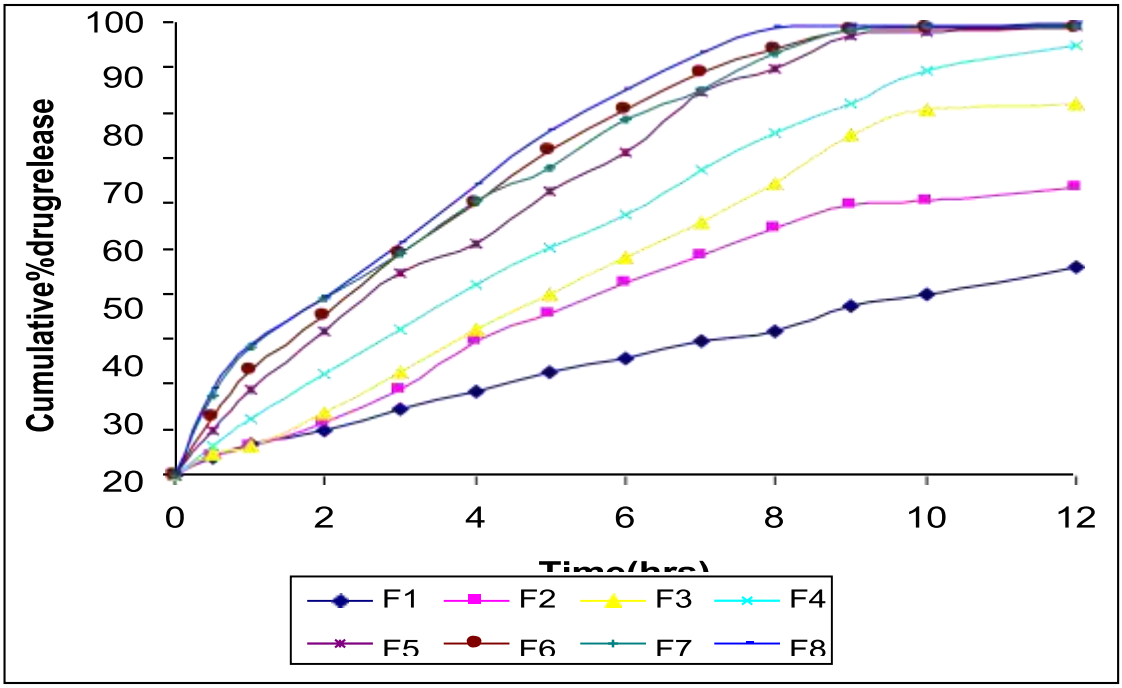
RELEASE KINETIC

Medication discharge design was assessed in 0.1 N HCl and phosphate cradle pH 6.8. Delivery pace of F1, F2, F3 details were discovered to be moderate and inadequate in both disintegration medium. It was discovered that medication discharge rate expanded by diminishing and expanding the proportion of Chitosan. Energy and instrument of medication discharge from all definition was assessed based on zero request, Higuchi condition and Peppa's model. Connection coefficient (r2) and slop an incentive for every condition was determined from Microsoft dominate. Zero request plots for all details were discovered to be line are in both disintegration medium. That demonstrates it might follow zero order component.

Table: RELEASE KINETICSOFMICROSPHEREIN PHOSPHATE BUFFER pH6.8

Formulation	Zero Order		Higuchi Equation		Peppa's Equation	
	r^2	K_0	r^2	K_H	r^2	n
F_1	0.997	3.761	0.978	13.73	0.920	0.776
F_2	0.982	5.92	0.973	21.84	0.937	0.795
F_3	0.984	7.65	0.965	27.69	0.941	0.746
F_4	0.991	8.29	0.982	30.54	0.890	0.693
F_5	0.969	8.84	0.987	33.49	0.843	0.610
F_6	0.950	8.67	0.988	33.04	0.794	0.614
F_7	0.955	8.31	0.992	32.43	0.784	0.572
F_8	0.937	8.44	0.985	33.02	0.771	0.572

ZERO ORDER PLOT FOR ALL FORMULATION IN PHOSPHATE BUFFER pH6.8



CONCLUSION

The present study aimed at developing a microsphere of glimepiride using natural polymer for a longer duration of action. Drug polymer interaction study performed by FTIR spectra and DSC Thermogram revealed non-reacttivity and feasibility of formulations. Different batches of complex were formulated by changing their molecular ratio and subsequent batches of microspheres were prepared using w/o emulsion method through ionotropic gelation mechanism. Nine experimental batches of microspheres loaded with drug and Chitosan (CM) were prepared and comparatively evaluated for several characterizing parameters like Particle size, percentage yield, percentage drug entrapment, percentage Accelerated stability studies.

Preliminary data showed the percentage cumulative drug was released in 24 hours study was 50% in 8 hours ,80% in 22 hours and 95% after 24 hours for M6 proving efficiency toward control of drug release and it was further treated for kinetic analysis to investigate release pattern and release mechanism, it followed non-fickian release mechanism.

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After careful comparison, batch M6 having all promising evidences of performances evaluated because this batch of GLM-CHI microspheres were prepared from 0.2 wt % of alginate and 0.3% chitosan in polymer solution having the polymer mass ratio GLM/CHI = 35/65 and these conditions were responsible for good particle stability and properties reported previously.

Therefore, it was selected for further part of study featuring enteric coating of microspheres, preparation and evaluation matrix tablet using M6 batch of microspheres. The optimized batch (M6) microspheres were selected for entric coating and formulated to prepare matrix tablets by wet granulation method. The dissolution profile showed that the rate of drug release was 0.86±0.08 % after 2 hours in SGF, 14.29±0.26 % after next 4 hours in SIF, 86.18±1.01% after next 18 hours in SCF rendered sufficiently controlled drug release pattern following first order sustainable release and satisfactory *in vitro* stability all of which were considered as a potential candidate that could be explored further to design of matrix tablet with enteric coated microsphere for colon targeting purpose.

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