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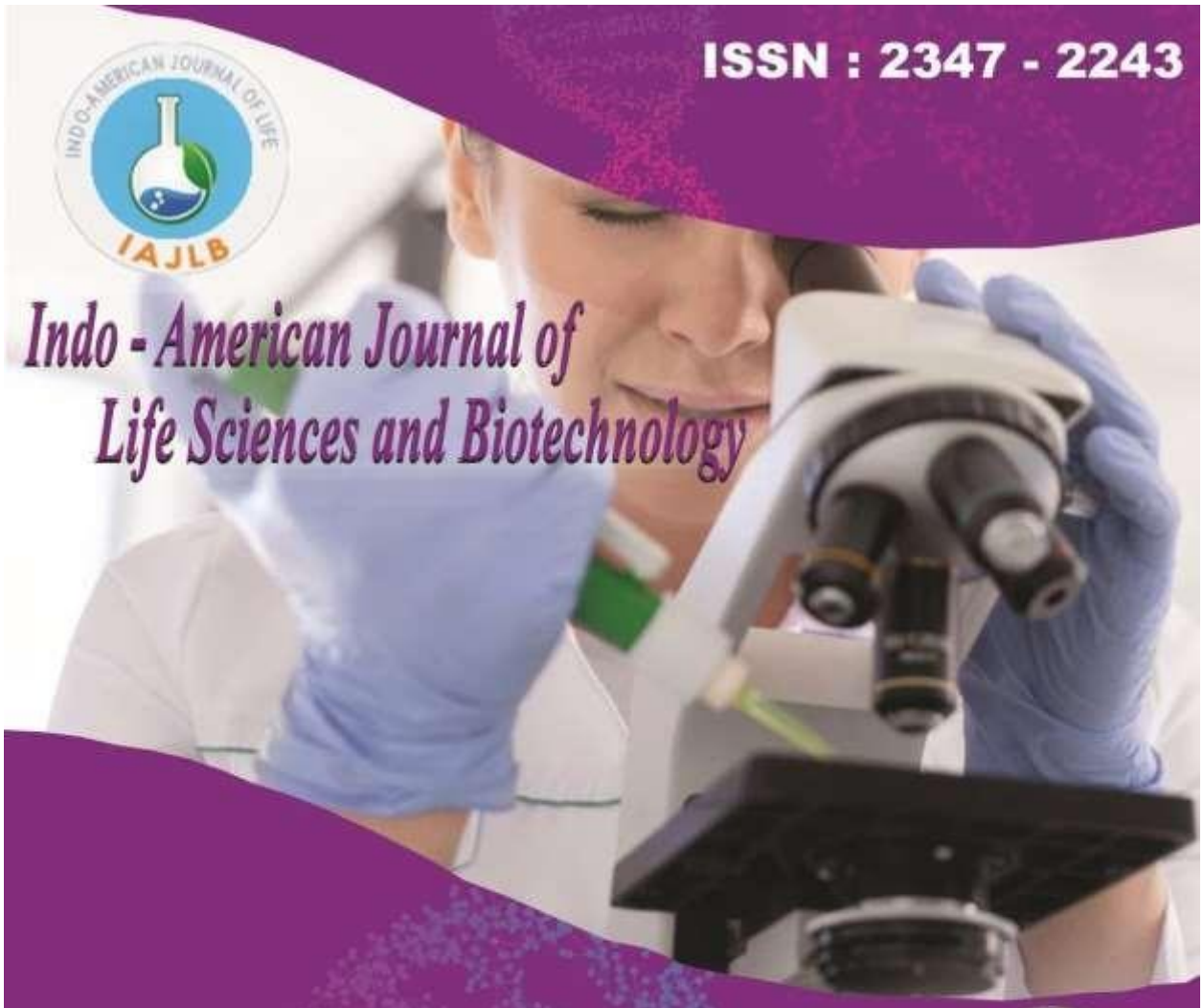

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DESIGN AND EVALUATION OF AMISULPRIDE LOADED CHITOSAN MICROPARTICLES

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ABSTRACT:

Amisulpride is an atypical antipsychotic drug with dopamine (D2 /D3) receptor blocker activity. The oral bioavailability of amisulpride was below 48% due to first pass metabolism and poor aqueous solubility. Amisulpride is a BCS Class II drug .The objective of this study is to develop controlled release formulation with lower dose of drug to uphold plasma concentration that may upturn patients compliance, enhanced therapeutic efficacy, Better Bioavailability and abridged side effects because of alteration in delivery pattern via slow release of drug from microparticles. The present research work was aimed at development and optimization of Amisulpride loaded microparticles with Chitosan natural polymer by using emulsification crosslinking and Ionotropic Gelation techniques. Total 8 formulations were designed, among those F1 to F4 are prepared by emulsification crosslinking method with chitosan as natural polymer for controlled release and different concentrations of TPP (As crosslinking agent), and F5 to F8 formulations are prepared by Ionotropic Gelation technique with same composition. All the formulations are subjected to their characterization like size analysis, flow properties, % Drug Content, % Encapsulation Efficiency, Wall thickness, SEM Analysis, IR Sprectroscopy and evaluation for invitro drug release studies. From this study it was found that the microparticles formulated with Ionotropic gelation method and Emulsification Crosslinking method techniques showed significant differences in their release rate and permeability coefficient values. Emulsification Crosslinking method was found to be more suitable for sustained release as it yielded slow release of the Amisulpride and offered Improved Bioavailability.

Keywords: Amisulpride, ionotropic gelation, Emulsification Crosslinking, *in-vitro* wash off test, Microparticles. microcapsulation efficiency.

INTRODUCTION:

Schizophrenia is the most common form of severe mental illness, with a lifetime risk of developing the disease of about 1% [1]. There is no cure available for schizophrenia. Traditional or typical antipsychotic drugs (neuroleptics), such as chlorpromazine and haloperidol, appear to act centrally by blocking dopamine (D) receptors in the brain. As a group, they relieve symptoms in at least 75% of patients during an acute attack [2].

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Amisulpride is another atypical antipsychotic agent, structurally similar to sulpiride. It differs from other atypical in that it exhibits selective affinity for dopamine D2and D3receptors only. The effectiveness of amisulpride in improving both the positive and negative symptoms of schizophrenia probably relates to its different effects on dopaminergic transmission at high and low doses [3,4] . To characterize the role of the 5-HT7receptor in the antidepressant effects of amisulpride, a study Prepared 5- HT7receptor knockout mice. These results indicate that 5-HT7 receptor antagonism plays a major role in the antidepressant effects of amisulpride [5]. Amisulpride and its relative sulpiride have been shown to bind to and activate the GHB receptor at doses that are used for therapeutic purposes [6].Amisulpride 400-1200mg/day was found to be as least as effective. At low doses amisulpride demonstrated a similar safety profile to placebo. At higher doses adverse events such as endocrine effects, agitation, insomnia and anxiety occurred at a similar r ate to that seen with other antipsychotics. It has no affinity for serotonergic alpha-adrenergic, H1 histaminergic or cholinergic receptors. Amisulpride acts preferentially on presynaptic receptors increasing dopaminergic transmission at low doses [7]. There are two absorption peaks - one hour post-dose and a second 3-4 hour s after taking the tablet. The elimination halflife is 12 hours. Absolute bioavailability is 48%. Amisulpride is weakly metabolized by the liver. There are two inactive metabolites. The drug is mainly eliminated unchanged by the kidney. 50% of an IV dose is eliminated by the kidney of which 90% is eliminated in the first 24 hours. Drug absorption is rapid, within 3-4 hours of oral administration and to improve patient compliance, a once-daily sustained-release formulation of Amisulpride is desirable. The principal aim of the investigation undertaken is to develop a micro particulate drug delivery systems for an antipsychotic drug such as Amisulpride. To reduce the dosing frequency and to improve patient compliance prolonged release dosage forms are required. Hence, there is a scope for continued interest and need for developing controlled release formulations. In the present investigation Amisulpride loaded chitosan microparticles were prepared by emulsification crosslinking Crosslinking and Ionotropic Glation with an objective of developing microparticles for oral controlled release. Chitosan is the second most abundant natural polymer after cellulose obtained by deacetylation of chitin. Chitosan possess some ideal properties of polymeric carriers for nanoparticles such as biocompatible, biodegradable, nontoxic and inexpensive. These properties make chitosan a very attractive material as drug delivery carriers. Chitosan nanoparticles are prepared by the emulsification based on the interaction between the negative groups of sodium tripolyphosphate (TPP) and Rendering positively charged amino (-NH2) and hydroxyl (-OH) groups, CS enables a high degree ofchemical modification.

MATERIALS:

Glibenclamide (Medley Pharmaceuticals Ltd., Daman Unit), Chitosan, (Qualigens; Mumbai), sodium trypolyphosphate (Qualigens; Mumbai), Acetic acid (Qualigens; Mumbai), Peanut oil (Qualigens; Mumbai), **Chitosan** (Qualigens; Mumbai)**,** glutaraldehyde(Qualigens; Mumbai), span 80 (Qualigens; Mumbai), liquid paraffin(Qualigens; Mumbai).

PREPARATION OF MICROPARTICLES:

Amisulpride microparticles prepared by Emulsification Cross linkingmethod:

400mg of Amisulpride was added into 50mlof 2%acetic acid solution containing 2000mg of chitosan with magnetic stirrer to form water phase. 250*ml* of liquid paraffin and 2.5 *ml* of Span-80 were mixed by stirring at room temperature to form oil phase. Then total of 50*ml* water phase was dripped into above oil phase at a speed of 40-60 drops per minute. The mixture was emulsified at 1500*rpm* stirring speed until stable emulsion formed. To crosslink and separate the microparticles 20 ml of various concentrations of Trypolyphosphate (10-25mg/ml) in aqueous solution was added to the system. This was done by slowly adding with a micropipette. The stirring was continued for about 1hr. The preparation was then centrifuged at 2000 rpm and then the supernatant was decanted. The microparticles at the bottom was collected and washed with the petroleum ether. Then the washed microparticles were air dried and stored in desiccators. [5]

Amisulpride microparticles prepared by Ionotropic gelation method:

Solutions were prepared by dissolving Chitosan (50ml of 1.5 % W/V) and various concentrations of Trypolyphosphate (10-25mg/ml) in aqueous solution of acetic acid(2%v/v), and in double distillled water respectively. 20ml of Trypolyphosphate aqueous solution was added drop wise into 50m of chitosan solution containing 400mg of Amisulpride. The stirring was continued for about 1hr. The preparation was thencentrifuged at 2000 rpm and then the supernatant was decanted and the microparticles at the bottom was collected. Then the microparticles were air dried and stored indesiccators[5].

Amisulpride microparticles prepared by Emulsification Crosslinking method:

Solutions were prepared by dissolving Chitosan (50 ml of 1.5 % W/V) in aqueous solution of acetic acid (2%v/v). The 400mg of Amisulpride was added to the polymer solution and mixed thoroughly. The dispersed phase was then added drop wise through a 10 ml pipette into a continuous phase consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 ratio containing 0.5% surfactants span 80 to form a (w/o) emulsion. Stirring was continued for 15 min and then the various concentrations of glutaraldehyde (10- 25% v/v) was added drop wise at regular intervals of time and stirring was continued for 1 hours after addition of glutaraldehyde. The preparation was then centrifuged at 2000 rpm and then the supernatant was decanted and the microparticles at the bottom was collected. Then the microparticles were air dried and stored in desiccators[6].

Table 1: Composition of Amisulpride Microparticles:

Emulsification Crosslinking Method			Ionotropic gelation method		
Formulation Code	**Chitosan concentration(% w/v) (polymer)**	**TPP concentration(% w/v) (crosslinking agent)**	**Formulation Code**	**Chitosan concentration(% w/v) (polymer)**	**TPP concentration (% w/v) (crosslinking agent)**
F-1	2.5	1	F-5	2.5	1
F-2	2.5	1.5	F-6	2.5	1.5
F-3	2.5	2	F-7	2.5	2
F-4	2.5	2.5	F-8	2.5	2.5

CHARACTERIZATION OF MICROPARTICLES

Size Distribution and Size Analysis [7]: For size distribution analysis, 250 mg of the microcparticles of different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed. The mean particle size of the microcapsules was calculated by the formula.

$$\text{MeanParticleSize} = \frac{\sum(\text{MeanParticleSizeof theFractionX WeightFraction})}{\sum(\text{Weight Fraction})}$$

Evaluation of Flow Properties: The flow properties of different microparticles were studied by measuring the angle of repose employing open tube method (2.3 cm diameter) method. The angle of repose was calculated by using the following formula[7].

$$\text{Tan}\,\theta = \frac{h}{r} \quad \text{or} \quad \theta = \text{Tan}^{-1}\frac{h}{r}$$

Where h = height of the pile, cm r = radius of the base of the pile, cm

Bulk Density:[7] The bulk density was determined by measuring the volume occupied by the preweighed microcparticles. It was calculated with the formulae.

$$\text{Bulkdensity} = \frac{\text{Mass of microparticles}}{\text{bulk Volume}}$$

Tapped Density:[7] Accurately weighed 10 g of the beads and transferred in to 25 ml measuring cylinder. It was subjected to tapping for 3 times and the volume occupied by the beads was noted. Tapped Density is estimated by using the following formula[9].

$$\text{Tapped Desity} = \frac{\text{Weight of the microparticles}}{\textbf{Bulk volume of microparticles}}$$

Carr's Index:[7] The percentage of compressibility of microspheres was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio:[7] Hausner ratio of microparticles was determined by comparing the tapped density to thebulk density using the formulae.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Wall Thickness: Wall thickness of micro particles was determined by the method of Luu et al using

$$h = \frac{r(1 - p)d1}{3[pd2 - (1 - p)d1]}$$

the equation[8].

Where h is the wall thickness

r is the arithmetic mean radius of the micro particles

d_1 is the density of the core material

d_2 is the density of the coat material

p is the proportion of the medicament in the microparticles

Estimation of drug content of Amisulpride microcparticles[8]: Accurately 100 mg microparticles were weighed and transferred in to a mortar. Powdered and dissolved in 100 ml of pH 7.4 phosphate buffer, suitably diluted the absorbance of the resulting solution was measured at 228 nm[9].

Entrapment Efficiency of Glibenclamide microcparticles[8]:

Entrapment efficiency[10] was calculated using the formula.

$$\text{Entrapment efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

Estimated percent drug content was determined from the analysis of 100 mg microparticles and the theoretical percent drug content was calculated from the employed core:coat ratio in the formulation of microparticles.

Drug Release Studies of Amisulpride microparticles[9]:

Release of Amisulpride from the microparticles, was studied in phosphate buffer of pH 7.4 (900 ml) using Eight Station Dissolution Rate Test Apparatus (M/s. Electrolab) with a paddle stirrer at 100 rpm[11] and at 37 ^{O}C ± 0.5 ^{O}C. A sample of microparticle (equivalent to 5 mg of Amisulpride) was used in each test. Samples were withdrawn through a filter (0.45) at different time intervals and were assayed at 228 nm for Amisulpride using Shimadzu double beam UV spectrophotometer. The drug release experiments were conducted in triplicate[12].

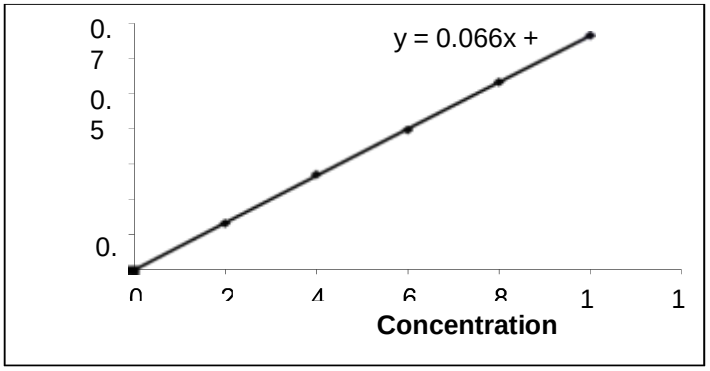
SEM Analysis: The samples for the SEM analysis were prepared by sprinkling the microparticles on one side of the double adhesive stub[13]. The stub was then coated with fine gold dust. The microparticles were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 10kv[14].

RESULTS:

Table 2: Calibration Values for the for the estimation of Amisulpride in 7.4 phosphate buffer[15]:

CONCENTRATION (□g/ml)	ABSORBANCE ($\bar{X}$ ± s. d.)
0	0
2	0.133±0.06
4	0.271±0.11
6	0.397±0.08
8	0.532±0.06

Figure 1: Calibration Curve for the estimation of Amisulpride in 7.4 phosphate buffer:



10	0.664 ±0.05

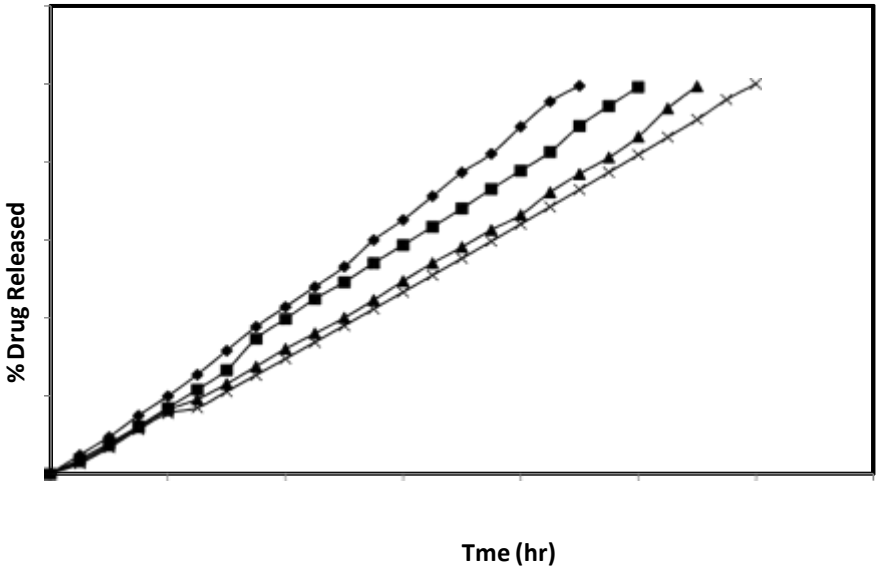
Table 3: Physical Properties of Amisulpride microparticles Prepared by Emulsification Crosslinking method[16]:

Formulation	Angle of Repose	Bulk density g/cm^3	Tapped Density	Carr's Index	Hausner's ratio	Avg Particle size (µm)	% Drug Content	% Enacapsulation Efficiency
F-1	26.37	0.350 ±0.013	0.408± 0.011	14.21±0.022	1.161±0.014	149.26	12.86	94.34
F-2	25.65	0.320 ±0.022	0.370± 0.009	11.89±0.009	1.134±0.017	144.32	11.83	94.67
F-3	22.76	0.319 ±0.005	0.362± 0.021	11.87±0.017	1.130±0.024	188.37	11.11	96.42
F-4	21.13	0.276 ±0.014	0.314± 0.013	12.10±0.024	1.137±0.012	179.56	10.40	97.16

Table 4: Release Data of Amisulpride microparticles Prepared byEmulsification Crosslinking method:

S.No	Time (h)	Percentage of Amisulpride Released ($\bar{x}$ ± sd)			
		F1	F2	F-3	F-4
1.	0	0	0	0	0
2.	0.5	3.54±0.12	2.75±0.16	4.21±0.12	3.47±0.15
3.	1	7.68±0.23	6.84±0.23	6.30±0.32	5.85±0.16
4.	1.5	12.46±0.36	11.23±0.35	10.95±0.21	10.40±0.13
5.	2	18.62±0.21	15.91±0.25	15.36±0.26	14.53±0.19
6.	2.5	24.26±0.25	20.61±0.16	17.16±0.16	17.98±0.17
7.	3	30.27±0.29	27.62±0.32	22.07±0.19	20.14±0.22
8.	4	36.51±0.23	35.63±0.34	26.53±0.11	24.33±0.21
9.	5	40.10±0.35	38.71±0.26	31.03±0.21	28.54±0.13
10.	6	45.62±0.15	45.81±0.12	35.00±0.22	32.77±0.26
11.	7	52.07±0.39	48.12±0.29	38.99±0.26	37.02±0.26
12.	8	57.87±0.18	53.00±0.25	45.55±0.23	40.30±0.25
13.	9	66.07±0.28	59.64±0.15	48.41±0.21	45.60±0.22
14.	10	70.12±0.16	64.29±0.26	53.01±0.12	51.92±0.21
15.	11	78.20±0.35	66.98±0.23	57.10±0.16	54.26±0.19
16.	12	80.96±0.27	71.95±0.21	61.49±0.19	58.63±0.15
17.	13	87.91±0.24	75.68±0.15	65.35±0.16	62.02±0.32
18.	14	93.36±0.16	83.44±0.36	70.13±0.23	69.43±0.14
19.	15	96.39±0.19	88.12±0.13	74.85±0.24	73.87±0.23
20.	16	-	93.21±0.18	80.06±0.12	76.32±0.32
21.	17	-	97.05±0.11	85.38±0.18	80.80±0.11
22	18	-	-	93.32±0.32	85.31±0.15
23	20	-	-	96.27±0.14	89.83±0.19
24	22	-	-	-	93.92±0.22
25	24	-	-	-	97.95±0.17

Figure 2: Release Profiles of Amisulpride microparticles Prepared by Emulsification Crosslinking method



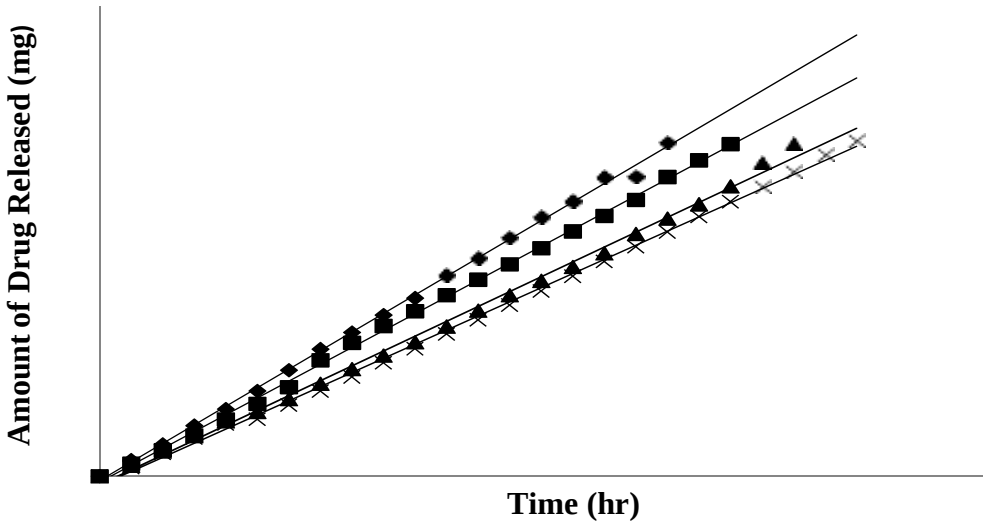
(-■-) **Amisulpride Microparticles prepared with 1%W/V crosslinking agent**

(-✦-) **Amisulpride Microparticles prepared with 1.5%W/V crosslinking agent**

(-▲-) **Amisulpride Microparticles prepared with 2%W/V crosslinking agent**

(-×-) Amisulpride **Microparticles prepared with 2.5%W/V crosslinking agent**

Figure 3: Zero Order Plots of Amisulpride microparticles Prepared byEmulsification Crosslinking method



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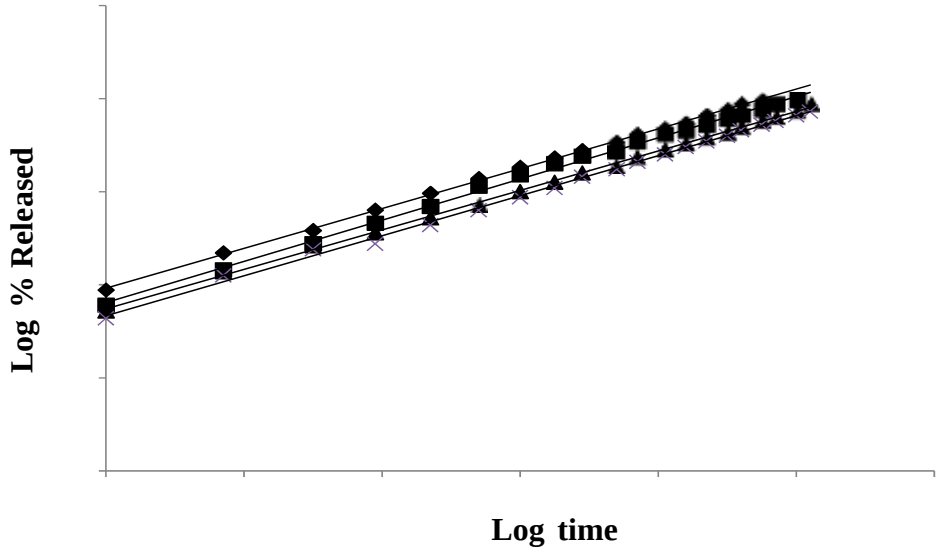
(-✦-)**Amisulpride Microparticles prepared with 1.5%W/V crosslinking agent**(-▲-)**Amisulpride Microparticles prepared with 2%W/V crosslinking agent**

(-×-) **Amisulpride Microparticles prepared with 2.5%W/V crosslinking agent**

Figure 4: Peppas Plots of Amisulpride microparticles Prepared byEmulsification Crosslinking method



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(-×-)**Amisulpride Microparticles prepared with 2.5%W/V crosslinking agent**

Figure 5: Correlation ship between Wall Thickness and Release Rate Constant of Amisulpride microparticles Prepared by Emulsification Crosslinking method

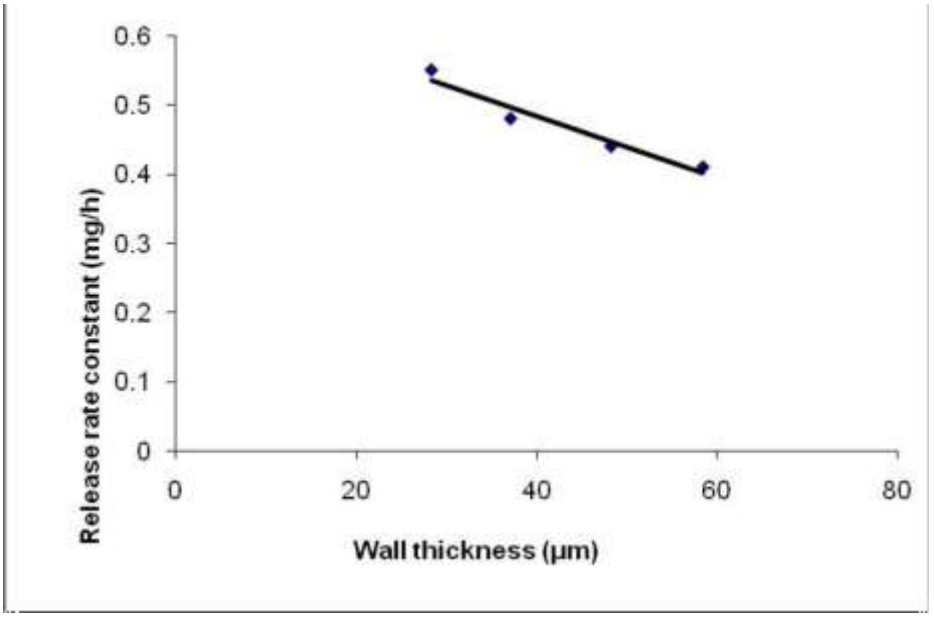


Table 5: Release Kinetics of Amisulpride microparticles Prepared by Emulsification Crosslinking method

Formulation	Correlation Coefficient Values (R^2)				Release Rate Constant (mg/hr) Ko	t50 %	t90 %	Wall Thickness(µm)	N Value
	Zero Order	First Order	Higuchi Model	Peppas Model					
F-1	0.9992	0.7949	0.9128	0.9998	0.55	4.6	8.2	28.37	1.0591
F-2	0.9990	0.8165	0.9135	0.9993	0.48	5.1	9.2	37.13	1.1013
F-3	0.9974	0.7757	0.9031	0.9994	0.44	5.9	10.6	48.26	1.0791
F-4	0.9980	0.6792	0.9034	0.9988	0.41	6.2	11.1	58.43	1.1032

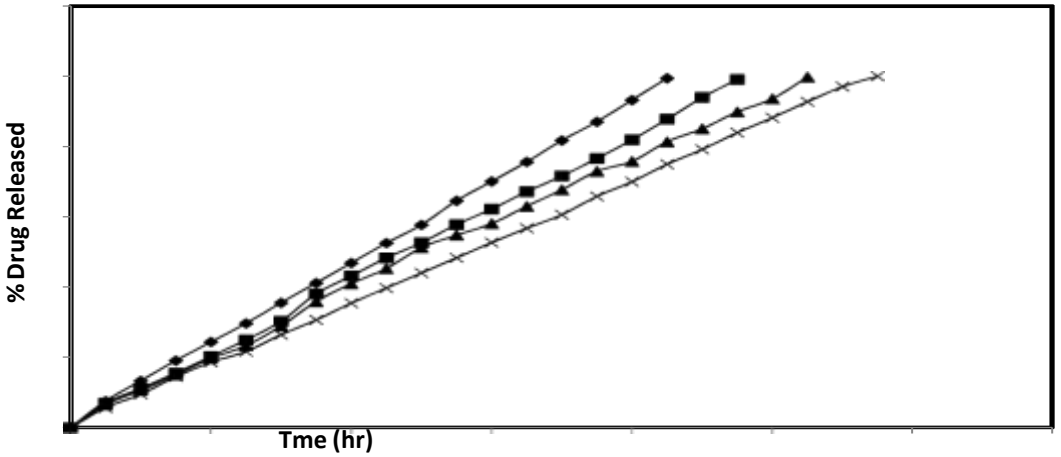
Table 6: Physical Properties of Amisulpride microparticles prepared by Ionotropic gelation method:

FormulationCode	Angle of repose	Bulk Density (g/cm^3)	Tapped density	Carr's Index	Hausner's Ratio	Average Particle Size (µm)	% Drug Content	% Encapsulation Efficiency
F-5	27.35	0.251±0.024	0.216±0.011	15.240±0.019	1.106±0.019	165.23	12.75	94.85
F-6	25.39	0.304±0.015	0.266±0.019	15.207±0.027	1.125±0.011	179.56	11.84	95.24
F-7	25.17	0.245±0.025	0.391±0.005	13.37±0.024	1.122±0.014	185.45	10.99	94.97
F-8	23.86	0.323±0.027	0.387±0.014	12.750±0.017	1.123±0.027	199.64	10.37	95.59

Table 7: Release Data of Amisulpride microparticles prepared by Ionotropic gelation method

S.No	Time (h)	Percentage of Amisulpride Released ($\bar{x}$ ± sd)			
		F-5	F-6	F-7	F-8
1.	0	0	0	0	0
2.	0.5	6.05±0.13	5.01±0.16	4.79±0.18	7.65±0.15
3.	1.0	12.89±0.16	10.12±0.18	9.57±0.19	10.48±0.19
4.	1.5	18.26±0.18	14.52±0.19	15.97±0.16	15.42±0.20
5.	2.0	23.72±0.17	22.22±0.16	21.67±0.13	19.57±0.23
6.	2.5	28.81±0.19	25.94±0.15	25.30±0.17	23.65±0.16
7.	3.0	34.77±0.16	29.23±0.23	30.86±0.21	27.39±0.25
8.	4	40.19±0.23	35.00±0.25	36.80±0.20	29.60±0.22
9.	5	45.35±0.24	45.09±0.19	39.88±0.23	34.64±0.16
10.	6	51.43±0.21	51.21±0.26	46.17±0.24	39.93±0.15
11.	7	58.60±0.23	54.54±0.22	49.12±0.26	45.24±0.11
12.	8	63.42±0.12	58.71±0.24	55.65±0.23	49.57±0.16
13.	9	68.92±0.21	64.09±0.31	58.93±0.22	55.65±0.18
14.	10	74.46±0.23	68.04±0.20	64.85±0.13	61.48±0.14
15.	11	80.56±0.20	73.47±0.26	68.53±0.21	66.69±0.12
16.	12	85.88±0.17	75.47±0.12	74.78±0.15	70.84±0.0.13
17.	13	94.04±0.13	79.76±0.22	78.61±0.13	75.83±0.21
18.	14	97.24±0.17	85.62±0.15	83.17±0.11	80.02±0.23
19.	15	-	93.79±0.16	87.86±0.17	84.78±0.24
20.	16	-	96.90±0.18	90.65±0.19	87.03±0.12
21	17			95.38±0.21	89.56±0.17
22	18			97.56±0.26	93.85±0.14
23	20				97.80±0.11

Figure 6: Release Profiles of Amisulpride microparticles prepared by Ionotropicgelation method



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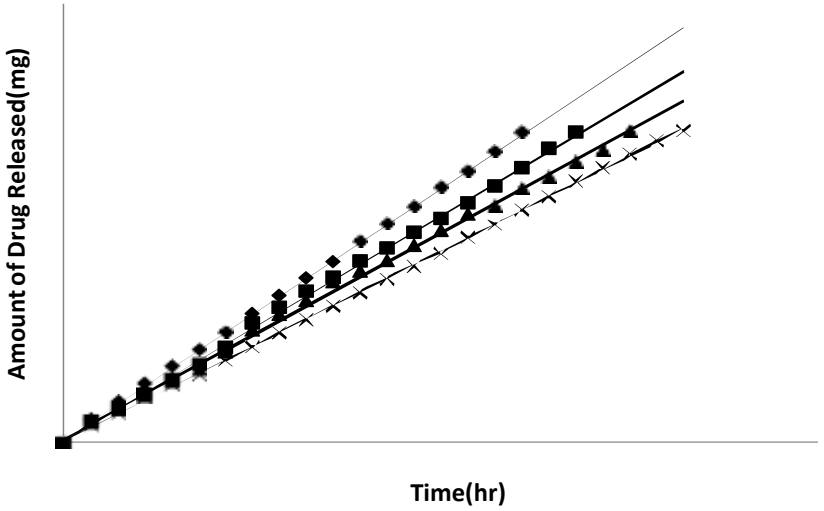
(-×-)**Amisulpride Microparticles prepared with 2.5%W/V crosslinking agent**

Figure 7: Zero order Plots of Amisulpride microparticles prepared by Ionotropicgelation method



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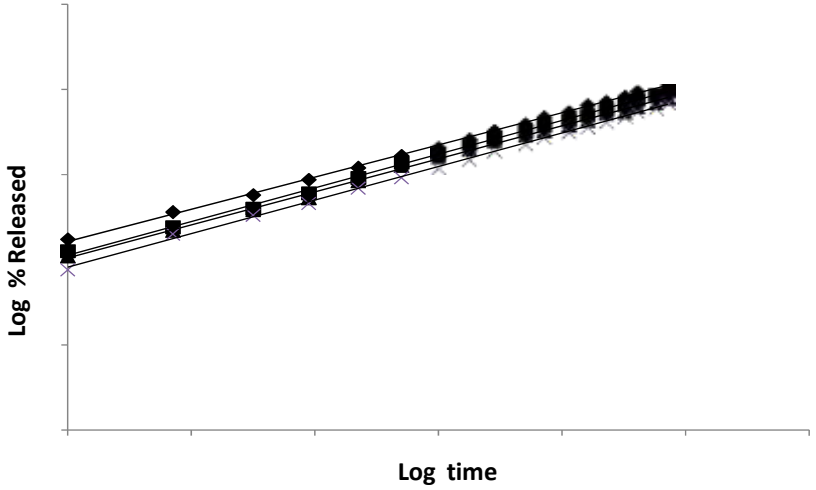
(-▲-)Amisulpride **Microparticles prepared with 2%W/V crosslinking agent**

(-×-)**Amisulpride Microparticles prepared with 2.5%W/V crosslinking agent**

Figure 8: Peppas Plots of Amisulpride microparticles prepared by Ionotropic gelation method



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(-▲-)Amisulpride **Microparticles prepared with 2%W/V crosslinking agent**

(-×-)**Amisulpride Microparticles prepared with 2.5%W/V crosslinking agent**

Figure 9: Correlation ship between Wall Thickness and Release Rate Constant of Amisulpride **microparticles prepared by Ionotropic gelation method**

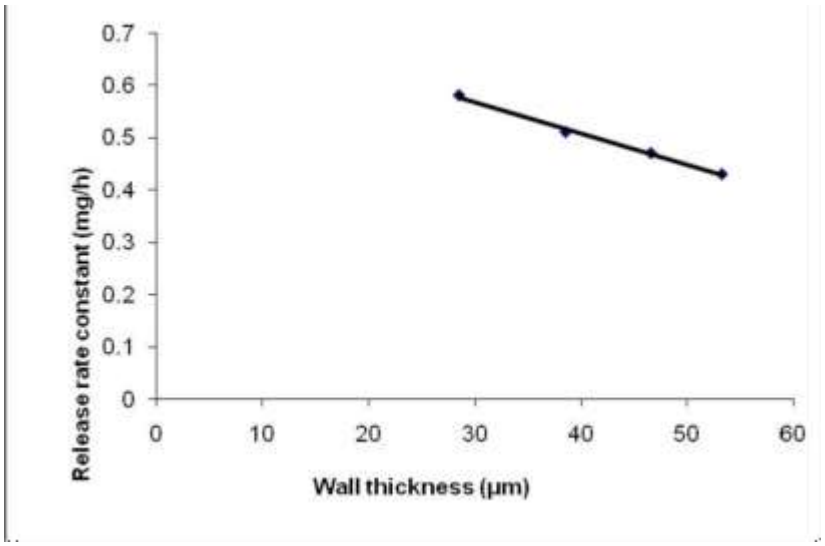
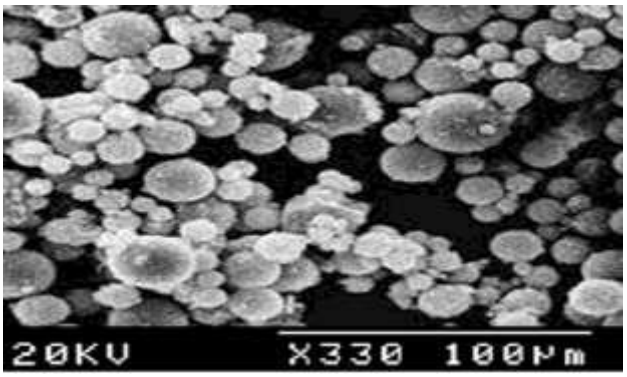


Table 8: Release Kinetics of Amisulpride microparticles prepared by Ionotropic gelation method

Formulation Code	Correlation Coefficient Values(R^2)				Release Rate Constant (mg/hr) Ko	t_{50} %	t_{90} %	Wall Thickness (µ)	n Value
	Zero Order	First Order	Higuchi Model	Peppas Model					
F-5	0.9997	0.8049	0.9292	0.9992	0.58	4.3	7.7	28.54	0.9213
F-6	0.9994	0.8241	0.9260	0.9973	0.51	4.8	8.7	38.56	0.9403
F-7	0.9987	0.7905	0.9326	0.9983	0.47	5.2	9.4	46.62	0.9333
F-8	0.9998	0.7651	0.9239	0.999	0.43	5.7	10.3	53.29	0.9438

Figure 10: Scanning Electron Microscope Photograph of Amisulpride microparticles prepared by Emulsification Cross linking method



RESULTS AND DISCUSSIONS:

Amisulpride microparticles Prepared by Emulsification Crosslinking method.

The microparticles were Prepared by Emulsification Crosslinking method by using chitosan as polymer and various concentrations of Trypolyphosphate (10-25mg/ml) in aqueous solution as cross linking agent. The method employed gave discrete, spherical, non-sticky and free flowing microparticles. As aggregates these microparticles were also non-sticky and free flowing. The formation of a stable emulsion in the early stages is important if discrete microparticles are to be isolated. An optimal concentration of emulsifier is required to produce the finest stable dispersion. Below optimal concentration the dispersed globules/droplets tend to fuse and produce larger globules because of insufficient lowering in interfacial tension, while above the optimal concentration no significant decrease in particle size is observed, because a high amount of emulsifying agent increases the viscosity of the dispersion medium. The optimal concentration of **span 80** was found to be 1 %. Microscopic examination of the formulations revealed that the microparticles were spherical and appeared as aggregates or discrete particles. The particle size of the microparticles ranged between 149.26 and 179.56 μm. All formulations had a narrow particle size distribution.The mean particle size of microparticles was influenced by the concentrations of Trypolyphosphate used and its proportion in the formulation. The mean size increased with increasing concentrations of Trypolyphosphate. It would appear that increasing concentrations of Trypolyphosphate produced a significant increase in viscosity of the internal phase, thus leading to an increase of emulsion droplet size and finally a higher microparticle size.

These microparticles were characterized for size analysis, flow properties, % Drug Content, % Encapsulation Efficiency. The results are given in Table 3. All the formulations offered good flow property. The technique also showed good entrapment efficiency. The microparticles were subjected to *In-vitro* release studies by employing 7.4 pH phosphate buffer and the data was shown in Table 4 and Figure 2. When the amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microparticles followed zero order kinetics Figure 3. To ascertain the mechanism of drug release from various microcapsules plot of log %Released vs log time (peppas plots) were drawn. The plots were found to be linear (Figure4) with all microparticles. Release Kinetics of Amisulpride microparticles were shown in Table 4. The exponential coefficient (n) values were found to be in between 1.0591 to 1.1032 indicating supercase –II transport diffusion mechanisam. These results indicated that the release rate was found to decrease with increase in concentration of coating material applied. The wall thickness of microparticles was found to be increased with the increase in concentration of coating material applied. There exists a good correlation ship in between wall thickness and release rate constant Figure 5.

Amisulpride microparticles Prepared by Ionotropic gelation method

The microparticles were prepared by Ionotropic gelation method by using chitosan as polymer and various concentrations of Trypolyphosphate (10-25mg/ml) in aqueous solution as cross linking agent. The method employed gave discrete, spherical, non-sticky and free flowing microparticles. As aggregates these microparticles were also non-sticky and free flowing. Microscopic examination of the formulations revealed that the microparticles

were spherical and appeared as aggregates or discrete particles. The particle size of the microparticles ranged between 165.23 and 199.64μm. The mean particle size of microparticles was influenced by the concentrations of Trypolyphosphate used and its proportion in the formulation. The mean size increased with increasing polymer concentration. It would appear that increasing polymer concentration produced a significant increase in viscosity of the internal phase, thus leading to an increase of emulsion droplet size and finally a higher microparticle size. These microparticle s were characterized for size analysis, flow properties, % Drug Content, % Encapsulation Efficiency. The results are given in Table 7. All the formulations offered good flow property. The technique also showed good entrapment efficiency. The microparticles were subjected to *In-vitro* release studies by employing 7.4 pH phosphate buffer and the data was shown in Table 7 and Figure 6. When the amount of drug release values were plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these microparticles followed zero order kinetics Figure 7. To ascertain the mechanism of drug release from various microparticles plot of log % Released vs log time (peppas plots) were drawn. The plots were found to be linear (Figure 8) with all microparticles. Release Kinetics of Amisulpride microparticles were shown in Table 8. The exponential coefficient (n) values were found to be inbetween 0.9213 to 0.9438.indicating non fickian mechanisam. These results indicated that the release rate was found to decrease with increase in concentration of coating material applied. The wall thickness of microparticles was found to be increased with the increase in concentration of coating material applied. There

exists a good correlation ship in between wall thickness and release rate constant Figure 9.

Influence of method of preparation on the release rate of drug frommicroparticles:

The microparticles formulated with Ionotropic gelation method and Emulsification Crosslinking method techniques showed significant differences in their release rate and permeability coefficient values. Emulsification Crosslinking method was found to be more suitable for sustained release as it yielded slow release of the drug glibenclamide and offered low permeability coefficient.

SEM Analysis:

Scanning electron microscopy of drug-loaded microparticles (Figure 10) shows that the obtained microparticles exhibited good spherical nature.

SUMMARY AND CONCLUSION:

The following conclusions were drawn from the results

1. The Emulsification Crosslinking method and Ionotropic gelation method used to produce microparticles gave discrete, spherical, non-sticky and free flowing microparticles.
2. The optimal concentration of surfactant (**span 80)** was found to be 1. %. The use of the surfactant permits the remarkable reduction in the size of the microparticles as the result of decrease in the interfacial tension.
3. All formulations had a narrow particle size distribution. The mean particle size of microparticles was influenced by the type of polymer used and its proportion in the formulation.
4. The mean size increased with increasing the concentrations of Trypolyphosphate.
5. It was also found that

formulations prepared by Emulsification Crosslinking method released slower than those prepared by Ionotropic gelation method.

6. Among all the formulations microparticles prepared by Emulsification Crosslinking method with 2.5% crosslinking agent shown required controlled release for a period of 12 hours .

7. Drug release from all the microparticles followed zero order kinetics and controlled by peppas mechanism. Good correlationship was observed in between wall thickness and release rate constant. The drug release from the microparticles depended on the percent coat material and the polymer employed in the preparation.

8. Scanning electron microscopy of drug-loaded microparticles shows that the obtained microparticles exhibited good spherical nature.

9. FTIR studies indicate that there were no chemical incompatibility between drugs and the polymers used.

Reference :

1. Schizophrenia: The forgotten Illness.SANE Mental Health Series No.1.

2. Anon. The drug treatment of patients with schizophrenia. DTB 1995; 33(11): 81-86.

3. Anon. Solian, 1997.Summary of Product Characteristics. Lorex Synth labo Ltd.

4. Coukell AJ, Spencer CM & Benfield P,1996. Amisulpride: A review of its pharmacodynamic and pharmaco-kinetic properties and therapeutic efficacy in the management of schizophrenia. CNS Drugs; 6: 237-256.

5. Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth B, 2009. Amisulpride is a potent 5-HT (7) antagonist: relevance for

antidepressant actions in vivo. Psychophar macology (Berl).

6. Maitre M, Ratomponirina C, Gobaille S, HodY, Hechler V (Apr 1994). "Displacement of [3H] gammahydroxybutyrate binding by benzamide neuroleptics and prochlorperazine but not by other antipsychotics". Eur J Pharmacol. 256 (2): 211- 4. Satheesh Madhav N.V, Shivani Kala. Review on Microparticulate Drug Delivery System. International Journal of PharmTech Research. 2011; 3(3):1242-1254.

7. Boyer P, Lecrubier Y,Stalla Bourdillon A, Fleurot O, 1999 Amisulpride versus amineptine and placebo for the treatment of dysthymia. Neuropsychobiology; 39:1, 25-32.

8. Hammad ume1, Hemlata Nigam, Asif M Tamboli, M. Sundara Moorthi Nainar. Microencapsulation: Process, Techniques and Applications. International Journal of Research in Pharmaceutical and Biomedical Sciences.2011;2(2) :474-482.

9. Nitika Agnihotri, Ravinesh Mishra, Chirag Goda, Manu Arora. Microencapsulation – A Novel Approach in Drug Delivery: A Review. Indo Global Journal of Pharmaceutical Sciences, 2012; 2(1): 1-20

10. Dashora, K.; Saraf, S.; Saraf, S. Effect Of Processing Variables On Micro Particulate System Of Nimesulide. *The Chinese Pharm. J.*,2006 ; 58:. 67-74.

11. Goto S, Komatsu M, Tagawa K, Kawata M, Preparation and evaluation of gelatine microcapsules of sulfonamides. Chem. Pharm. Bull., 1983; 31: 256–261.

12. Nixon J R and Meleka M R, The preparation and characterisation of ethylcellulose-walled theophylline microcapsules, J. Microencap., 1984; 1: 53–64.

13. Friend D R, Polyacrylate resin microcapsules for taste masking of antibiotics. J. Microencap., 1992; 9: 469–480.

14. Tirkkonen S, Turokka L and Paronen P. Microencapsulation of indomethacin by gelatin–acacia complex coacervation in the

presence of surfactants. J. Microencap., 1994;11: 615–626.

15. Berkland C, Kim KK, Pack DW. Fabrication of PLG microspheres with precisely controlled and monodisperse size distributions. J Control Rel 2001; 73(1): 59-74.

16. Harnish K. Patel , Priyanka R. Patel, Tushar J. Brahmbhatt1, Satvik S. Bhatt . Sustained Release Microparticles: A Review . American Journal of PharmTech Research 2011; 1(4): 108-126.