Table 5: Evaluation parameters of factorial design batch CS–BR microspheres

Batch code	% Drug Release (± SD) (12 hr)	% Drug release (± SD) (24hr)	Particle size (µm) (± SD)	EE (%) (± SD)	Swelling index (± SD)
C1	82.34 ± 1.26	99.54 ± 1.32	460.54 ±12.36	62.23 ± 0.57	0.812 ± 0.042
C2	80.25 ± 1.43	96.81 ± 1.28	438.45 ±15.59	63.32 ± 0.53	0.788 ± 0.036
C3	78.30 ± 1.67	94.70 ± 1.21	396.56 ±14.37	62.63 ± 0.56	0.754 ± 0.055
C4	74.21 ± 1.73	91.25 ± 1.52	647.42 ± 7.23	68.28 ± 0.46	1.238 ± 0.036
C5	68.38 ± 1.42	89.64 ± 1.67	604.34 ± 7.83	67.93 ± 0.38	1.186 ± 0.049
C6	62.17 ± 1.12	79.50 ± 1.42	561.24 ± 5.18	62.56 ± 0.53	1.124 ± 0.051
C7	60.41 ± 1.76	82.44 ± 1.26	712.27 ± 4.21	83.92 ± 0.42	1.453 ± 0.042
C8	56.18 ± 1.81	77.56 ± 1.42	670.38 ± 4.52	82.81 ± 0.33	1.384 ± 0.033
C9	50.06 ± 1.18	63.92 ± 1.64	634.06 ± 3.86	78.36 ± 0.37	1.217 ± 0.045

Table 6: Micromeretic properties of factorial design batch CS–BR microspheres.

Batch Code	Bulk Density (g/cc) (± SD)	Tapped Density (g/cc) (± SD)	Angle of Repose (θ^0) (± SD)
C1	0.534 ± 0.045	0.649± 0.023	24.36 ± 2.23
C2	0.546± 0.032	0.618 ± 0.053	24.41 ± 2.06
C3	0.561 ± 0.048	0.659 ± 0.035	23.33 ± 2.16
C4	0.532 ± 0.042	0.663 ± 0.048	25.76 ± 1.82
C5	0.538 ± 0.039	0.672 ± 0.052	26.32 ± 1.69
C6	0.576 ± 0.046	0.649 ± 0.046	27.46 ± 2.54
C7	0.587 ± 0.043	0.675 ± 0.028	26.21 ± 2.32
C8	0.529 ± 0.032	0.661 ± 0.035	27.42 ± 2.25
C9	0.548 ± 0.052	0.652 ± 0.026	26.89 ± 2.45

Hence the drug release in the simulated colonic fluid with cecal content may be a result of the combined effect of diffusion and erosion. From the result it is clear that the release profile of factorial design batch microspheres were in the order of C1>C2>C3>C4>C5>C6>C7>C8>C9. The concentration of polymer influenced the control of drug release for 24 hours. The stirring speed is inversely proportional to particle size, entrapment efficiency, swelling index and percent drug released. The concentration of polymer is directly proportional to the particle size, swelling index and drug entrapment efficiency which might be due to formation of denser network upon addition of cross-linking agent and presence of higher molecular weight polymer, bora rice in the formulation.

Formulation C2 showed 96.81% of drug release within 24 hours and its drug entrapment efficiency was 63.32%. The formulation C1 though showed higher percent of drug release i.e. 99.54% within 24 hour, its drug entrapment efficiency was 62.23% which is less than that of the formulation C2 for which it was not selected. Other formulations i.e. C3 to C9 showed lower percentage of drug release i.e. from 63.92 to 94.70% due to which they could not be selected as for once a daily dosage form maximum amount of drug should be released within 24 hours. Therefore though the formulation C3 to C9 should higher entrapment efficiency than that of the formulation C2, they could not be selected and the formulation C2 has only been selected for the further studies. The result is presented in Table 5 and Figure 8.

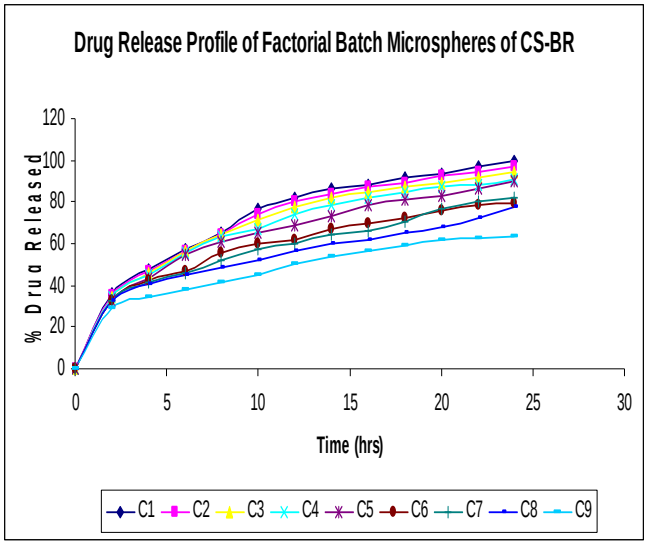

Fig. 8: *In vitro* dissolution study of factorial design batch CS–BR microspheres.

Kinetics of drug release: The release rate constant was calculated from the slope of appropriate equations and the correlation coefficient (R) was determined for all the formulations (Table 7). The release profile and the entrapment efficiency of formulation C2 was found to be satisfactory in comparison to other formulation, the discussion on the kinetics of other formulations was not considered further.

In vitro drug release of C2 was best explained by k-peppas equation with highest linearity (R_p =

Table 7: Analysis of *in vitro* dissolution data of factorial design batch CS–BR microspheres.

Batch Code	C1	C2	C3	C4	C5	C6	C7	C8	C9
Zero order									
R_0	0.7240	0.7169	0.7146	0.6911	0.7059	0.6512	0.7421	0.6500	0.6574
K_0	5.2208	5.1000	5.0961	4.8049	4.6053	4.1718	4.1112	3.8070	3.3455
1st order									
R_1	0.9389	0.9944	0.9754	0.9863	0.9807	0.9395	0.9678	0.9242	0.8873
K_1	-0.1638	-0.1338	-0.1389	-0.1058	-0.0947	-0.0743	-0.0737	-0.0628	-0.0500
Higuchi									
R_h	0.9855	0.9852	0.9850	0.9832	0.9858	0.9782	0.9867	0.9740	0.9764
K_h	21.9911	21.4922	21.4775	20.2747	19.4126	17.6292	17.2725	16.0700	14.1215
k-Peppas									
R_p	0.9931	0.9981	0.9941	0.9958	0.9973	0.9977	0.9915	0.9935	0.9905
K_p	27.2602	26.9692	26.9447	26.5308	25.5030	25.2808	24.2931	24.9344	21.6135
n_p	0.5199	0.5219	0.5275	0.5319	0.5387	0.5412	0.5425	0.5478	0.5476
Hix.Crow.									
R_h	0.9818	0.9700	0.9688	0.9382	0.9350	0.8775	0.9280	0.8657	0.8304
K_h	-0.0334	-0.0304	-0.0307	-0.0261	-0.0241	-0.0201	-0.0198	-0.0175	-0.0145

0.9981), followed by Higuchi's equation, (R_h = 0.9852) and First order (R_1 = 0.9944). This indicates that the drug was diffused from polymeric matrix. The drug release was found to be closed to Higuchi kinetics which indicates that the drug diffuses at a comparatively slower rate as the distance of diffusion increases.

Stability study of the optimized factorial design batch formulation of glipizide:

The optimized formulation (C2) was evaluated for difference factor (f_1) and similarity factor (f_2) of dissolution rate study after 3 months of storage at accelerated condition (40 ^{0}C ± 2 ^{0}C and 75% ± 5% RH), the results of which are shown in Table 8 and Figure 9. The dissolution profile of the formulation at initial stage was considered as reference for calculation of dissimilarity factor (f_1) and similarity factor (f_2). When the value of f_2 lies between 50 to 100 and f_1 is less than 15, the two dissolution profiles (test and reference) are considered to be similar. The results obtained (Table 8) revealed that the dissolution profile of formulations after 3 months of storage at accelerated condition was similar with the initial dissolution profile of formulation. Based on the results it was considered that the formulation is stable after 3 months of storage at accelerated stability conditions.

Table 8: Evaluation of CS-BR microspheres (C2) after 3 months of storage at 40 ^{0}C ± 2 ^{0}C and 75% RH ± 5% RH

Parameter	Initial	One month	Two months	Three months
f_1 value*	---	2.45	4.13	5.26
f_2 value*	---	86.58	79.57	74.22

*Initial sample (0 month) was taken as reference to calculate f_1 and f_2 values.

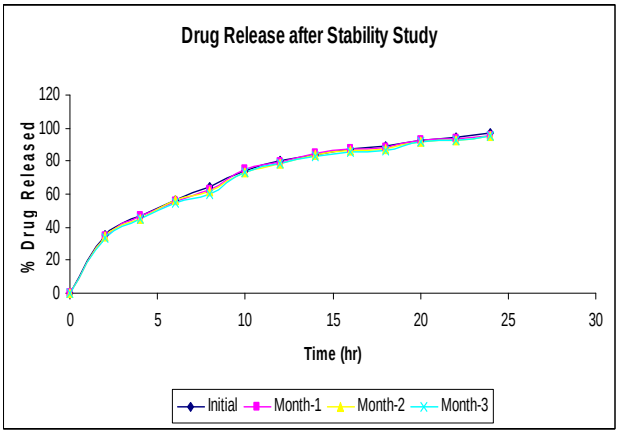

Fig. 9: *In vitro* dissolution profile of the optimized formulation (C2) after subjected to stability study

CONCLUSION:

The results of study clearly indicate that there is a great potential in delivery of glipizide to the colonic region. Study showed that the manipulation of polymer concentration and stirring rate influence particle size of microspheres, sphericity and flow property of microspheres. From the above study it concluded that high concentration of Bora Rice will retard the drug release, may be due to high content of amylopectin present in the bora rice. Formulation C2 is the best formulation for controlling the drug release to the colon. Hence from the above study it concluded that high amylopectin containing bora rice, natural polysaccharide showed potential for controlled release colon targeting drug delivery.

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