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Research Article

DEVELOPMENT AND EVALUATION OF TOPICAL GEL OF CURCUMIN FROM DIFFERENT COMBINATION OF POLYMERS FORMULATION & EVALUATION OF HERBAL GEL

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ABSTRACT

The present study was aimed to develop topical gel of Curcumin which enhances the bioavailability & permeation with the help of combination of polymers which will be useful in further drug delivery. Polymers plays major role in various characterization parameters of topical gel such as *in vitro* release and rheological properties. A stable, elegant formulation of curcumin gel was successfully prepared, overcoming problems of bioavailability and in comparison to other polymers (such as Carbapol & Sodium alginate) combination of Carbapol and HPMC presented higher % of drug diffusion, good rheological & texture properties. The release rate of gel was found to obey Peppas model.

Keywords: Curcumin, Topical gel, Carbapol, Sodium Alginate, HPMC, *In vitro* release study.

INTRODUCTION

There have been concerns related to the conventional topical dosage forms such as lotions, creams, ointments and powder in terms of drug diffusion or release from the vehicle and delivery through the skin. Creams and Lotions often provide poor bioavailability of the drug because they are rapidly cleared from the skin and poorly release the drug from base. Non hydrophilic ointments are oleaginous, greasy and are non convenient to patients and also medicated powders for topical application have short residence time on the skin. Gels are semisolid systems in which the movement of the dispersion medium is restricted by interlacing three dimensional network of particles or solvated macromolecules of dispersed phase. The increased viscosity caused by interlacing and consequently internal friction is responsible for the semisolid state. Also a gel may consist of twisted matted strands often tied together by stronger types of Vander Waals Forces to form crystalline and amorphous regions throughout the system[1]. The use of gel as a delivery system can increase the residence time of drugs on the skin and consequently enhance bioavailability. Gel delivery systems have several advantages such as the ease of administration, non greasy, patient compliance, high residence time on the skin and better drug release. Curcumin (CUR) a constituent of Curcuma longa (Family – Zingeberaceae) chemically known as diferuloulmethane has been reported to possess antioxidant, anti-inflammatory ant carcinogenic and hypocholesterolemic properties. Curcumin has also been shown to counter inflammatory responses similarly to the action of steroids, but without side effects[2]. Following oral administration (up to 8g per day) it is poorly absorbed and only the traces of compound appear in blood.

It undergoes extensive first pass metabolism and hence is a suitable candidate for topical gel formulation[3]. Among polymers used for formulation of gel base is combination of CRB and HPMC, combination of CRB and Sodium Alginate, alone CRB to describe physical properties, rheological behavior and to determine the amount of drug diffused better. These polymers have several attributes as a gelling agent like high viscosity at low concentration and give pleasant texture, do not support bacterial or fungal growth and are non irritating. A ideal penetration enhancer should have no pharmacological activity in body, should work rapidly, nontoxic, nonirritating, no allergic, should be suitable for formulation into topical formulation and should be compatible with drug and excipient[4]. Menthol affects the skin permeation by dual mechanism: by forming a eutectic mixture with the penetrating compound, herby increasing its solubility and by altering the barrier properties of the stratum corneum[5]. Cyclic monoterpenes generally showed stronger enhancement of curcumin than other terpenes and flavanoids[6]. Menthol causes cooling sensation that mask pain, local anesthetic effects and being penetration enhancer, it increases the skin permeation of the drug substances[7]. The aim of the study is to develop a curcumin topical gel formulation employing combination of CRB and HPMC, CRB and Sodium Alginate, alone CRB at different ratios compare their release.

MATERIALS AND METHODS

Curcumin (Lobe Chemicals), Carbapol 940(Magus Chemicals) Sodium Alginate (Oswald Scientific store) HPMC (Oswald Scientific store) and other ingredients used were of analytical grade. Double distilled water was used throughout the study.

Preparation of gels by simple dispersion method

The composition of different gel formulations is shown in Table No.1.Carbapol 940 was soaked overnight in purified water containing Sodium benzoate 0.2% w/v. HPMC/Sodium Alginate Solution was prepared & homogenised it at 3000rpm in tissue homogenizer. Then drug solution was prepared with ethanol and Propylene Glycol in glass stopper vial. Drug solution was transferred in HPMC /Sodium Alginate/CRB solution and homogenized. Then Polymer drug solution was transferred in carbapol solution & neutralized it with triethanolamine followed by homogenization. Similarly for other formulation, drug polymer mixture was transferred to CRB solution in ratio of Drug: Polymer 1:1, 1:2, 1:3 [(CRB: HPMC): CUR], [(CRB): CUR], [(CRB: Sodium Alginate): CUR]

Table 1: Table shows the composition of topical gel formulations with different conc. of Different combination of polymers (%w/w)

Ingredients	Ratio 1:1			Ratio 1:2			Ratio 1:3		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC	1	---		2	---	---	3	---	---
Carbapol 940	1	1	2	2	2	4	3	3	6
Sodium Alginate	---	1	-	---	2	---	---	3	---
Curcumin	2	2	2	2	2	2	2	2	2
Propylene Glycol	5	5	5	5	5	5	5	5	5
Ethanol	15	15	15	15	15	15	15	15	15
Sodium benzoate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Triethanolamine for pH 7	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled Water q.s to make	10	10	10	10	10	10	10	10	10

RESULTS AND DISCUSSIONS

The gels were subjected to physical evaluations such as homogeneity, Grittiness, extrudability, pH, drug content, in vitro release and results are shown in Table No. 2.

Batches F1, F2, F3 with ratio 1:1 show best homogeneity & extrudability.During our physic-chemical evaluation studies all the formulations were within pH range (6.9-7.2). Different gel formulations were found to contain 98.5 -99.6% curcumin. Drug: Polymer ratio 1:1 results better % release than other proportions. Drug conc. was constant at 2% and the conc. of polymers increases which decrease *in vitro* drug release .Hence on the basis of analyzing all these parameters ratio 1:1 (Drug: Polymer) were selected. All 9 batches had drug solubilisation problem. As curcumin has good solubility in DMSO so DMSO was incorporated to selected 3 batches then evaluated with parameters as shown in Table No. 3

Drug release increased with addition of DMSO as percent cumulative release of F1 was increased from 62 to 85% and F2 was increased from 52 to 76%. Whereas for F3 it was raised from 48 to 62%. (Table 3) DMSO is one of the earliest and most widely studied penetration enhancing materials. DMSO alone has been applied topically to treat inflammation Although DMSO is an excellent accelerant, it does create problems.DMSO can cause denaturing of some skin proteins results in erythematic, scaling, contact urticaria, stinging and burning sensation[8].Individual chemicals are however limited in their efficacy in disrupting the skin barrier at low concentration and usually cause skin irritation at higher concentration[9].Hence menthol was incorporated to avoid side effects of alone DMSO & evaluated with same parameters as shown in Table No. 4

Rheology Study [10]

The rheological behaviour of all gel formulations 1, 2, 3 were investigated. The viscosity of different gel formulations was compared as shown in Table No.5

Table 2: Table shows Physicochemical Characters of these all Gel formulations

Formulations	Homogeneity	Grittiness	Extrudability	pH	Drug Content	Percentage release
F1 (1:1)	+++	-	+++	7.2	99.6	62
F2(1:1)	+++	-	+++	7.1	99.25	52
F3(1:1)	+++	-	+++	6.9	96.8	48
F4(1:2)	++	-	++	7.0	96	54
F5(1:2)	++	-	++	7.0	99.1	43
F6(1:2)	++	-	++	7.0	98.9	36
F7(1:3)	+	-	+	7.2	98.7	44
F8(1:3)	+	-	+	7.1	99	34
F9(1:3)	+	-	+	7.0	98.5	28

+ Satisfactory, ++ good, +++ very good, - no grittiness

Table 3: Table shows Physicochemical Characters of selected 3 batches after adding DMSO

Formulations	Homogeneity	Grittiness	Extrudability	pH	Drug Content	Percentage release
F1	+++	-	+++	7.2	98	85
F2	++	-	++	7.1	97.5	76
F3	+	-	+	7.0	99.4	62

Table 4: Table shows Physicochemical Characters of selected 3 batches after adding Menthol

Formulations	Homogeneity	Grittiness	Extrudability	pH	Drug Content	Percentage release
F1	+++	-	+++	7.2	98	97
F2	+	-	+	7.1	97.5	86
F3	++	-	+	7.0	99.4	70

Table 5: Table shows Viscosity values of Curcumin gels

Speed (rpm)	Viscosity [Pa·s] F 1	Viscosity [Pa·s] F2	Viscosity[Pa·s] F 3
5.16	28	25	20
10.1	16.9	11.8	11
15.1	12.5	7.15	6.21
20.1	10.3	5.13	5
25.2	8.76	3.71	0.106
30.2	7.75	2.08	0.235
35.1	7.04	1.84	0.133
40.1	6.38	1.58	0.345
45.3	5.93	1.36	0.358
50	5.69	1.22	0.373
55	5.23	1.08	0.417
60.2	4.87	0.944	0.394
65	4.51	0.856	0.328
70	4.26	0.784	0.298
75.2	3.99	0.689	0.302

The data in Table No. 5 indicates that F1 showed highest viscosity between 3.39 Pascal to 28 Pascal whereas F2 showed less viscosity between 0.689 Pascal to 25 Pascal whereas F3 showed least viscosity between 0.302 Pascal to 20 Pascal.All the formulations exhibited pseudo plastic flow; however no evidence of thixotropy was observed as given in Figure 1, 2 and 3

Figures 1, 2, 3 interpret Flow behaviour & Viscosity values. All obey pseudo plastic flow but F1 shows higher flow power value & correlation coefficient. Application of the power law model to the rheological properties of each formulation enabled the calculation of the consistency (k) and flow index (n). The values of flow index (n) were found to be less than one for all the gels confirming the shear thinning behaviour of all the gels. The same is also confirmed from plots of viscosity *vs.* shear rate indicating that the viscosity of the system decreased with increase in shear rate.The gels did not break even at shear rate of 500 indicating good gel strength. The values of flow index for F1 was highest (0.483) followed by F2 (0.38), F3 (0.32) High flow index reflects the mobility of the gel from the container. The values of consistency index & correlation coefficient for F1 was found to be higher than F2 & F3

F 1 [Combination of Carbapol & HPMC with ratio of 1:1 (Drug: Polymer 1:1)]

[1(CRB+ HPMC): 1CUR]

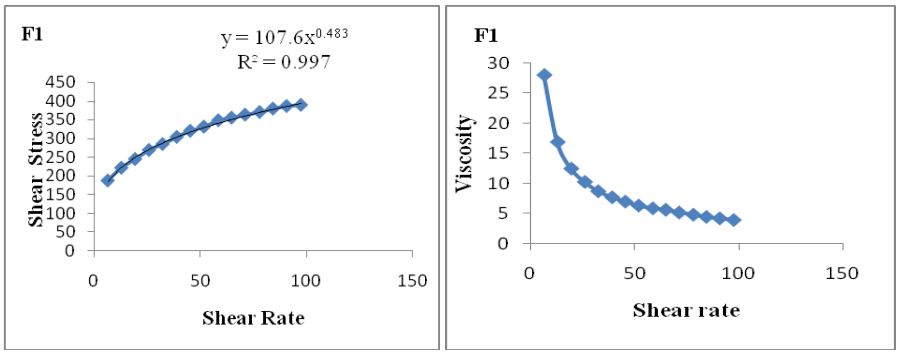

Fig. 1a: Shear rate versus Shear stress Fig. 1b: Shear rate versus Viscosity

F 2 [Alone Carbapol with ratio of 1:1(Drug: Polymer)]

[1(CRB):1CUR]

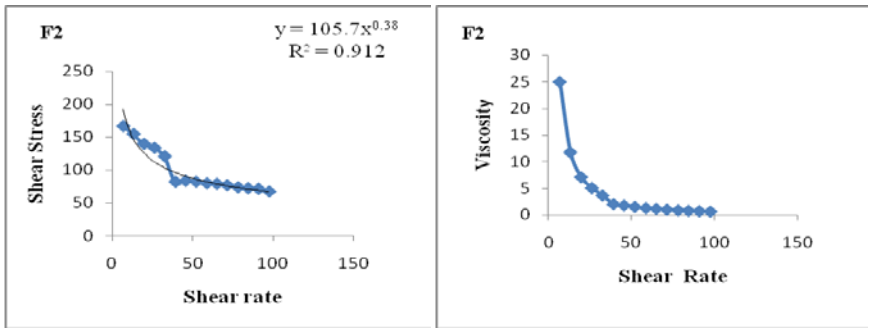

Fig. 2a: Shear rate versus Shear stress Fig. 2b: Shear rate versus Viscosity

F 3 [Combination of Carbapol & Sodium Alginate with ratio of 1:1 (Drug: Polymer)]

[1 (CRB + Sodium Alginate):1 CUR]

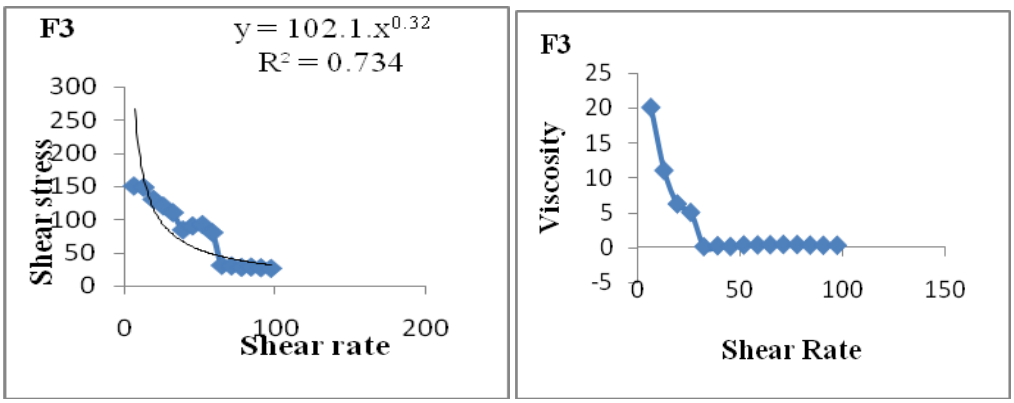

Fig. 3a: Shear rate versus Shear Stress Fig. 3b: Shear rate versus Viscosity

Texture Analyzer

The peak or maximum force is taken as a measurement of firmness; the higher the value, the more firm is the sample. The negative region of the graph, produced on probe return, is as a result of the weight of sample which is lifted primarily on the upper surface of the disc on return is shown in figure 4.

The maximum negative force is taken as an indication of the stickiness/cohesiveness of the sample. The more negative the value the more 'sticky' or 'cohesive' is the sample. Area of the negative region of the curve is often referred to as work of adhesion/viscosity. Higher is the value, more resistant to withdrawal is the sample, which is an indication of resistance to flow/viscosity of the sample as shown in Table No.6 which depicts the value, for TPA parameters for various gels of Curcumin.

The data in table 6 indicates that F1 is having maximum firmness, work of shear, stickiness and work of adhesion whereas F2 is having less firmness, work of shear and stickiness and work of adhesion whereas F3 is having least firmness, work of shear and stickiness and work of adhesion.

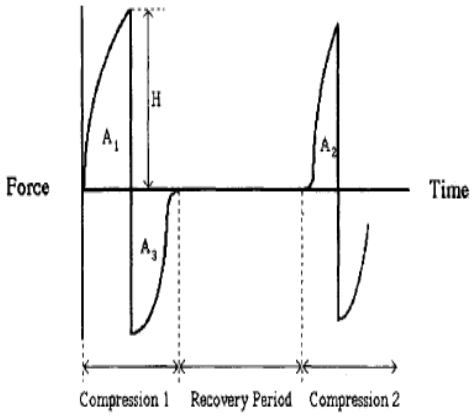

Fig. 4: Graphical output from texture profile analyzer

Table 6: Table shows properties of optimized gels (F1, F2, and F3)

Gel	Firmness (gm) +SD	Work of shear (gm.sec) +SD	Stickiness (gm) +SD	Work of adhesion (gm.sec) + SD	Cohesiveness	Gel Strength (gm $mm^{-1}sec^{-1}$)
F1	35.79+4.51	20.30+3.13	52.59+5.11	39.19+4.55	0.85+0.02	10.44+0.12
F2	34.12+3.42	16.98+2.97	32.90+4.63	32.79+3.49	0.84+0.03	7.78+0.22
F3	16.50+3.17	05.37+1.29	13.60+2.87	13.36+3.21	0.80+0.04	4.35+0.31

Table 7: Table shows Mathematical Models of optimized batches

Formulations	Zero Order	First Order	Higuchi	Hixson Crowell	Peppas	
	R^2	R^2	R^2	R^2	R^2	N
F1	0.993	0.727	0.887	0.876	0.999	1.160
F2	0.991	0.881	0.881	0.934	0.998	1.122
F3	0.989	0.933	0.874	0.976	0.997	0.997

Mathematical models for final batches [11]

The correlation coefficients of final formulations were compared in Table No. 7.

The drug release data were explored for the type of release mechanism followed. Release kinetic study of all formulation (F1 to F3) was studied (As Table No.4)or different kinetic equation (zero order, first order, Higuchi, Hixson Crowell & Peppas). The best fit with higher correlation (r^2 = 0.999) and release exponent (n=1.160) was found with the Peppas equation for F1 which indicate a indicates Super Case II transport. These n values are characteristic of super case II transport, suggesting that the contribution of polymer relaxation occurs throughout the entire dissolution period.

Stability Study[12]

The selected topical gel formulation F1 was subjected to stability studies for 3 months and were analyzed with following parameters as shown in Table No. 8

Table 8: Table shows stability study parameters of final batch

Parameters for Assessment	Initial	30 days	60days	90 days
Appearance	√	√	√	√
Homogeneity	√	√	√	√
Grittiness	√	√	√	√
Extrudability	√	√	√	√
pH	7.0	6.9	6.9	6.8
Drug Content	99.5 %	99.3 %	98.9 %	98.8 %
% Release	98.1 %	97.6	97.5%	97%

The experimental findings suggest that formulations F1 [(1(CRB: HPMC):1CUR)] was showed good stability and there is virtually no impact of change on the physical parameters of the selected curcumin gel formulation.

CONCLUSION

The percent drug diffused from gel formulations containing only one polymer such as CRB and combination of CRB + Sodium Alginate was low compared to formulation containing combinations of CRB + HPMC. The addition of HPMC to CRB enhanced the gel base properties. Formulations containing [1(CRB: HPMC):1CUR] gave gel of highest viscosity structure and best drug diffusion. It was observed that topical herbal gel prepared from combination of Synthetic & Semi synthetic polymers had maximum firmness, work of shear and stickiness and work of adhesion. Propylene Glycol not only acts as co solvent but also acts as stabilizer. Menthol not only avoids DMSO irritation but also gives cooling effect. Synergistic effect of DMSO & Menthol was showed in drug diffusion.

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